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USE OF GELATIN SOLUTIONS IN THE TREATMENT OF HUMAN SHOCK*

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The mechanism of shock is not completely understood. One of its recognized phenomena, however, is the reduction of the circulating plasma volume, due to either circulatory changes or to loss of plasma (local or into the tissues). In the latter case reduced plasma volume is associated with hemoconcentration.[23] Any attempt to rectify the decrease in plasma volume with or without hemoconcentration is considered rational in the treatment of shock.

Since crystalline solutions raise the plasma volume only temporarily[16,24] and are thus ineffective, colloidal substances have to be employed; the most suitable being human plasma or blood. Since these are not available in unlimited quantities, plasma substitutes are being developed from macromolecular substances.

The first of these substances to be widely used was gum acacia[4,14] which has been all but discarded because it is deposited in the liver.[2,18] In recent years pectin,[10,11,16,20] isinglass,[29,30] and gelatin[4,7,13,15] have been recommended as plasma substitutes. Within recent months several papers on the use of gelatin as a substitute for plasma in the treatment of experimental hemorrhagic and traumatic shock in dogs have appeared.[8,17,25] The present study deals with the results of treatment of shock in humans by the administration of gelatin solutions. Gelatin is a mixture of various proteins, varying in type and molecular size in

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different types of gelatins, depending upon source and preparation. It can be prepared as a non-toxic solution isotonic to plasma and somewhat more viscous than it. Experiments on rats, rabbits, and dogs carried out at the Upjohn Research Laboratories[31] have demonstrated that the gelatin solution used in these studies is well tolerated without toxic effects.

Method and Material. The material of this study constitutes 52 patients in shock of differing degree and etiology. To evaluate the effect of treatment, the severity of shock was classified arbitrarily, because reliable uniform clinical criteria do not exist. The following rough method of estimation is not proposed as a classification of shock for general use; however, it appeared useful in evaluating the effect of another solution we used for the treatment of shock.[22]

Mild. (1) Drop of systolic blood pressure not more than 30 mm. Hg as compared with the pre- or postshock level. (2) Increase in radial pulse rate.

Moderate. (1) Drop of systolic blood pressure more than 30 mm. Hg. (2) Decrease in volume of radial pulse with increase in rate. (3) Diaphoresis.

Severe. (1) Drop of systolic blood pressure more than 50 mm. Hg. (2) Barely palpable radial pulse ("thready"). (3) Cool clammy skin. (4) Restlessness.

Profound. (1) Blood pressure unobtainable. (2) Radial pulse unobtainable. (3) Rapid respiration. (4) Cold clammy skin. (5) Stupor. (6) Cyanosis.

Table 1 shows the type and degree of shock in the material examined.

In each shock patient, a record of the following clinical data was made: blood pressure, pulse, temperature, respiration and condition of the skin.

TABLE 1.—CLASSIFICATION OF THE 52 CASES OF SHOCK RECEIVING GELATIN ACCORDING TO ETIOLOGY AND SEVERITY

Type of shock	Degree of shock			
	Mild	Moderate	Severe	Profound
Postoperative	8	21	9	4
Traumatic	1	1	2	
Hemorrhagic	..	2	2	
Medical	..	..	..	2

Venous blood was obtained and placed in test tubes containing dried heparin.* A 5% solution of gelatin in normal saline was then intravenously administered, using the same needle with which the venous blood was drawn. The gelatin solution used in this study was prepared by the Upjohn Company, using a purified gelatin made from bone collagen. Calcium gelatinate prepared by electrodialysis was autoclaved, mixed with distilled water, sodium hydroxide, phenylmercuric borate and sodium chloride, passed through a sterilizing filter, and autoclaved again. The final product is a 0.9% sodium chloride solution containing approximately 5 gm. of gelatin in 100 ml. of solution. The pH is of physiologic range, the viscosity about 2 centipoises, and the oncotic pressure 70 mm. of mercury (± 5 mm.). The solution is preserved with 1:25,000 phenylmercuric borate. Total and non-protein nitrogen was determined on the final solution. Tests for sterility and for absence of pyrogens was carried out according to the U.S.P. XII.[27] In a period of 1½ or more hours 1000 cc. were usually given according to the severity of the shock. After infusion and 24 hours later, blood samples were drawn from the opposite arm and clinical data were checked.

In all blood samples the hemoglobin was measured with the photoelectric colorimeter.[12] The sedimentation rate was determined with the Wintrobe tube, the same tube being centrifuged after an hour for the hematocrit reading. The sedimentation rate was not corrected for change in red cell concentration.

* Provided by Roche-Organon, Inc. (Liquaemin), Nutley, N. J., and the Upjohn Company, Kalamazoo, Mich.

The density of the plasma as an index of the protein content was estimated with the falling drop apparatus of Barbour and Hamilton.[3] Non-protein, protein, and albumin nitrogen were determined by Nesslerization.[19] In the determination of the total protein nitrogen, as well as of the density of the plasma, the gelatin content has to be taken into consideration; further studies are planned to elucidate this relationship. The mean corpuscular hemoglobin concentration was calculated according to the following formula:[34]

$$\frac{\text{Hemoglobin in gm. per 100 cc. of blood}}{\text{Volume of packed cells in cc. per 100 cc. of blood}} \times 100$$

The normal mean averages 35% and varies from 33 to 38%.

Where a statistical evaluation was made, the t value was determined,*[6] indicating the statistical significance of the difference between pre- and post-treatment results. Values of t of 2.5 or over are considered to indicate a significant difference.

* $t = x/s/n$.

x = Mean of difference between the determinations before and after gelatin administration.

s = Standard deviation.

We are indebted to Miss Elizabeth M. Adles for the statistical evaluation.

Results. *I. Incidence of Reactions.* In none of the patients was there any evidence of pyrogenic or other untoward reaction to the gelatin administration. In none of them were chills, abrupt rise of temperature, or complaints of pain noted. A moderate rise of temperature (up to 2° F.) was occasionally seen, but could be explained by causes other than the gelatin administration (surgery, infections, etc.). No hemorrhagic tendencies were apparent. After the gelatin infusion, whole blood or plasma was repeatedly given without any complications. Some of the patients were under observation for over 1 month after gelatin administration and showed no sequelæ attributable to the administration.

II. Hemodilution. The mean of the hemoglobin, plasma density, total protein nitrogen, and hematocrit dropped markedly after the gelatin infusion and remained below control value for 24 hours (Table 2). The decrease was of statistical significance in all instances. The hemoglobin decreased slightly less and total protein nitrogen significantly less than the hematocrit.

TABLE 2.—INFLUENCE OF GELATIN ADMINISTRATION (IN 52 PATIENTS) ON THE BLOOD IN SHOCK

	Av. values prior to gelatin administration	Av. % change immediately after administration of gelatin	t value	Av. % change 24 hrs. after administration of gelatin	t value
Hematocrit	44%	−21.8	**16.7**	−15.8	**9.9**
Hemoglobin	13.7 gm./%	−17.9	**14.6**	−12.4	**10.3**
Protein nitrogen	6.7 gm./%	− 9.8	**7.0**	− 5.4	**3.2**
Plasma density	6.97 gm./%	−12.2	**14.1**	− 9.2	**9.9**
Non-protein nitrogen	31.7 mg./%	+ 4.5	1.6	+ 5.18	1.0

The decrease in the above factors varied in degree in different patients. Hematocrit, hemoglobin, and plasma density diminished in all patients immediately after the gelatin infusion, whereas the protein nitrogen increased in 6 cases. After 24 hours, there were increases in hematocrit, hemoglobin, and plasma density above the control level in 1 case each, and of the protein nitrogen in 11 cases. The albumin/

globulin ratio decreased from an average of 1.5 to 1.13 immediately after the infusion, the decrease being statistically significant; 24 hours later the average rose again to 1.42, however, without statistical significance (Table 3).

TABLE 3.—CHANGES IN SEDIMENTATION RATE, MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION, ALBUMIN/GLOBULIN RATIO, BLOOD PRESSURE, AND PULSE RATE AFTER ADMINISTRATION OF GELATIN TO PATIENTS IN SHOCK

	Av. values prior to gelatin administration	Av. change immediately after administration of gelatin	t value	Av. change 24 hrs. after administration of gelatin	t value
Sedimentation rate	29.2 mm./hr.	+25.6 mm.	**14.2**	+21.4 mm.	**10.9**
Mean corpuscular hemoglobin concentration	31.4%	+ 1.3%	1.9	+ 1.3%	**2.6**
Albumin/globulin ratio	1.5	− 0.37	**4.1**	− 0.08	0.5
Blood pressure:					
Systolic	77 mm. Hg	+42 mm. Hg	**10.8**	+45 mm. Hg	**9.3**
Diastolic	42 mm. Hg	+29 mm. Hg	**8.6**	+28 mm. Hg	**5.8**
Pulse	94.5/min.	0		+ 2.6	0.5

The non-protein nitrogen showed on the average an increase immediately and 24 hours later, but it was not statistically significant because of marked deviations in both directions.

III. Effect Upon Erythrocytes. The sedimentation rate which was, in the majority of cases, markedly elevated before treatment, consistently rose, the increase being statistically significant. The rise was maintained for 24 hours, and occasionally for 5 days. In general, in those cases in which the sedimentation rate had been markedly elevated to begin with, the rise after gelatin administration was proportionately less. This increase in the sedimentation rate was not influenced by dextrose, saline, blood, or plasma given following the gelatin.

The mean corpuscular hemoglobin concentration which, on an average, was originally below normal, rose consistently and was maintained for 24 hours, the increase at this time being of statistical significance.

TABLE 4.—THERAPEUTIC RESULTS FOLLOWING ADMINISTRATION OF GELATIN TO PATIENTS IN SHOCK

Degree of shock				
Mild	Moderate	Severe	Profound	
8	17	9	3	Gelatin solution alone relieved shock permanently
1	3	2	1	Shock relieved but blood also given for reasons other than shock (anemia, blood loss)
	2			Shock not relieved by gelatin but blood or plasma did relieve it
			1	Shock not relieved and patient expired
	1			Shock relieved only temporarily*
	1	2	1	Shock relieved but patient died of other causes

* This patient went into shock again the following day at which time a second infusion of 1000 cc. of gelatin relieved the shock permanently.

IV. Effect Upon Clinical Symptoms. The systolic and diastolic blood pressures, which were markedly reduced before treatment, rose

in all but 2 cases upon completion of the gelatin infusion and were maintained thereafter. The increase was statistically significant (Table 3). In 7 cases the blood pressure rose from zero to normal or near normal values. In patients with hypertension, the blood pressure was frequently restored to former hypertensive levels. Mathematical evaluations of the pulse changes were difficult because in 7 cases no radial pulse was present. In the rest of the cases which are listed in Table 3, no average change of the pulse rate was noted. Generally, an improvement in the character in the pulse was observed; changes in the skin from a cool clammy to a warm and dry condition were usually noted in those cases that responded.

Ordinarily, no consistent changes of temperature or respiration were encountered, excepting 1 case where the temperature rose 3° F. during the infusion; however, the underlying disease (abdominal carcinomatosis) may have been responsible for the rise.

V. Therapeutic Results. In the great majority of cases, one gelatin infusion relieved extreme as well as moderate shock, without any additional therapy (Table 4). In a few cases in whom gelatin had effectively relieved the shock, supplemental whole blood was administered for the treatment of an underlying anemia or profuse loss of blood. In 4 cases the gelatin did not relieve the shock, although in 2 patients blood or plasma infusion was successful (one associated with marked blood loss). In a third, (intestinal obstruction) both plasma and gelatin failed to prevent a fatal outcome; whereas a fourth went into shock again but was relieved by a second gelatin infusion. Four patients in whom the shock was relieved by gelatin, as seen from blood pressure response, died later from the following causes: burn toxemia in a diabetic, generalized peritonitis, bowel obstruction and ruptured esophageal varices.

VI. Repeated Administration. Gelatin administration was repeated in only 2 shock cases. One was a patient with surgical shock in whom a second liter of gelatin was necessary before shock was permanently relieved. A second case was that of a 50% burn of second degree; 2000 cc. of gelatin was given to treat the initial shock and then another 3000 cc. in the attempt to correct protein-deficiency. This patient, a diabetic, died on the 6th day, probably owing to toxemia.

Comment. The present study attempts to demonstrate the following points: 1. The administration of gelatin to patients in shock is a safe procedure. The only effect observed by us which has to be considered undesirable is the effect upon the erythrocytes. The increase of the sedimentation rate which is generally found upon injection of macromolecular substances was stressed by Ivy and his co-workers[15] as an important disadvantage in the use of plasma substitutes after marked hemorrhage. If the number of erythrocytes is reduced to begin with, a further reduction of functioning erythrocytes by pseudo-agglutination (rouleau formation) is dangerous. The increased sedimentation rate is caused by the rouleau formation.

No evidence was found that in cases of shock without severe hemorrhage this increased sedimentation rate was of clinical significance. The increase in rate was not more marked than that found in acute infection, and if the sedimentation rate would be corrected for the reduced red cell count (due to hemodilution), the rise of the sedimentation rate would appear even less marked. No signs of peripheral venous thrombosis were noted. The increase of the mean corpuscular hemoglobin concentration is probably the result of a slight shrinkage of the red blood cells. Absence of low degree of antigenicity of gelatin has been demonstrated previously,[26,28,33] as was also the fact that gelatin is not stored in tissues to a significant degree in contrast to other macromolecular substances.[14]

2. Gelatin solution is an effective hemodiluting agent. Part of its effect which is statistically significant is still encountered after 24 hours. The dilution of the red cells as judged from hematocrit and hemoglobin appears more marked than that of the plasma proteins. The values of both the total protein nitrogen and plasma density are influenced by the gelatin concentration in the plasma. The dilution of the plasma proteins is, therefore, more marked than can be interpreted from the determination of total protein nitrogen and plasma density. As gelatin influences the density of plasma to a different degree than the protein content, plasma density and protein nitrogen concentration run even less parallel than in other conditions. Since the protein of the gelatin is precipitated with the globulin fraction, a decrease of the albumin/globulin ratio may be anticipated. The non-protein nitrogen content of the gelatin may be responsible for the inconsistent increase of the plasma non-protein nitrogen; however, an exact evaluation is only possible if gelatin determinations are performed. For our present problem, the establishment of hemodilution suffices. The dilution of the plasma protein is not necessarily disadvantageous, since apparently not the plasma protein concentration but the total circulating plasma proteins are of significance.[1]

Gelatin solution was an effective agent in the treatment of shock of every type and degree in which we used it, probably because it produced hemodilution. A comparison with plasma and whole blood was not attempted in this preliminary study. The failures, however, were few enough to warrant a favorable comparison. The number of cases is sufficient, we believe, to exclude spontaneous recovery as a reason for this favorable response.

One thousand cc. of gelatin in the concentration used seems sufficient because only in 1 case was a second dose required.

This paper suggests that gelatin solutions have the required qualities of a plasma substitute. Whether its nitrogen content has nutritional value after intravenous administration in shock, as in experimental animals,[5,21,32] future investigations will have to decide. In view of the present shortage of plasma, gelatin may be a good substitute even if it should not be quite as effective as plasma itself.

Summary. Studies on 52 patients show that the administration of 1000 cc. of a 5% gelatin solution in normal saline was effective in the treatment of shock. It produced regularly a statistically significant hemodilution. No untoward effects were noted except an increase in the sedimentation rate, which, however, did not influence the clinical picture.

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XUM

INCREASES IN THE PLASMA VOLUME FOLLOWING THE ADMINISTRATION OF SODIUM SALTS*

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It has been demonstrated[8,10–12,15] that the plasma volume does not remain fixed even with mild dehydration and will decrease in proportion to the severity of the dehydration. In normal subjects dehydration, induced by the administration of a low salt diet and ammonium chloride[11] or by the intravenous administration of 2 cc. of mercupurine,[12] is associated with a significant fall in the plasma volume. Under these circumstances, it appeared that the plasma volume was not well supported by the extracellular fluid and that the loss of water and salt, coincident to the diuresis, was associated with the fall in plasma volume.

If the plasma volume is reduced by relatively small decreases in the body water, it would appear likely that the reverse situation would also be true. The administration of sodium salts sufficient to produce a positive sodium balance, along with sufficient water, should increase the volume of the extracellular fluid and presumably the plasma volume as well. These studies were undertaken to evaluate the effect of ingestion of large amounts of sodium salts with water *ad lib.* on the plasma volume of normal subjects.

Methods. Fourteen hospital patients in good health at the time of the observations, without evidence of cardiovascular or renal disease and who had never had edema, were selected as normal subjects. Each subject had been on the routine hospital diet with fluid and salt *ad lib.* for several days before the observations began and was presumably in a state of normal hydration.

The subjects were studied in two groups: the first received sodium bicarbonate and the second group was given sodium chloride. On the day the observations were started, the subject was weighed in the rested, postabsorptive state on a beam balance accurate to 2 gm. Following this, he rested on a table, and blood samples were taken for the determination of the plasma volume,[6] hematocrit,[21] and serum protein concentration;[2] stasis was rigidly avoided in all instances. A measurement of the antecubital venous pressure[13] was made during the blood sampling. In the first group, estimation of the hemoglobin concentration[5] and red blood cell counts were made on the oxylated blood samples taken for the hematocrit determination.

At the conclusion of the initial observations, the 6 subjects in Group I were given a liter bottle containing 25 gm. of sodium bicarbonate dissolved in 1000

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cc. of water. They were instructed to consume the contents of the bottle during the next 15 hours, taking 75 to 100 cc. per hour and to consume all the food on the diet trays. Each subject followed these instructions. All were permitted water *ad lib.* The following morning, the subject was again weighed and the initial observations were repeated. The same routine was again repeated, each subject consuming his usual diet and 25 gm. of sodium bicarbonate in 1000 cc. of water. The next morning after consuming 50 gm. of sodium bicarbonate in 48 hours in addition to his usual diet, the final observations were made.

The second group of 7 subjects were managed in exactly the same way except that 20 gm. of sodium chloride were given daily. The subjects were studied only after 48 hours on this régime and hemoglobin concentrations and red blood cell counts were not estimated.

One normal subject, R. C., the first to go on such a régime, received 40 gm. of sodium chloride daily for 2 days.

If the subject consumes his usual diet, significant changes in weight from one day to the next will reflect changes in the water content of the body. It can be assumed that changes in the weight of these subjects represents approximately the water held within the body. Certainly the error of such an assumption is of little significance in dealing with the relatively large and consistent changes in weight experienced by these subjects.

Twenty-two paired observations of the plasma volume repeated on successive mornings on control subjects in the rested, postabsorptive state, showed a mean variation from the initial value of +0.68%, S.D. 2.8%, S.E. ±0.61. The mean percentage change in hematocrit was −0.79%, S.D. 2.63%, S.E. ±0.56. In 13 control cases the variation in serum protein concentration was −0.60%, S.D. 3.49%, S.E. ±1.0. From these control studies, it would appear that variations in plasma volume greater than 5% would occur only 7 times in 100 subjects pursuing their usual routine.

Results. The changes in the plasma volume, hematocrit, hemoglobin concentration, red blood cell count, serum protein concentration, venous pressure, and body weight for all the subjects are recorded in Table 1. The percentage change expresses the variation in the plasma volume more accurately than the actual change, since the plasma volume varies considerably with the size of the individual.

It will be noted in Table 1 that the body weight progressively increased during the 2-day period in the group receiving sodium bicarbonate, though the greatest change in weight occurred on the first day. In both groups there was a similar and fairly consistent increase in the body weight averaging 1.56, ±0.36, or 2.3, ±0.17%, of the initial weight at the end of 2 days of sodium bicarbonate intake and 1.9, ±0.41 kg., or 3.1, ±0.73% of the initial weight at the end of 2 days of sodium chloride intake. There was also a close similarity between the increase in the plasma volume noted in both groups. The average increase in the plasma volume after the 2-day sodium bicarbonate period was 400 ±53.2 cc. or 14.4 ±1.54% of the initial determination, while the group receiving sodium chloride had an average increase of 440 ±35.5 cc. or 15.6 ±1.15% of the initial determination.

In both groups the change in the hematocrit reading and in the concentration of serum protein failed to reflect quantitatively the change in the plasma volume as measured by the dye method. The relative increase in the plasma volume in nearly every instance was considerably greater than the relative decrease in the hematocrit or serum protein concentration as measured by the percentage change.

TABLE 1.—CHANGES IN THE PLASMA VOLUME, HEMATOCRIT, SERUM PROTEIN CONCENTRATION, VENOUS PRESSURE AND BODY WEIGHT IN NORMAL SUBJECTS FOLLOWING THE ADMINISTRATION OF SODIUM SALTS

Patient	Change in plasma volume	Change in plasma volume (%)	Change in hematocrit	Change in hematocrit (%)	Change in serum protein	Change in serum protein (%)	Change in hemoglobin (%)	Change in red blood count (%)	Change in venous pressure	Change in body weight	Change in body weight (%)
After 25 Gm. of Sodium Bicarbonate in 24 Hours											
W. H.	..	..	−2.9	− 7.1	−0.38	− 5.7	− 8.2	− 7.2	+25.0	+1.73	+2.8
J. P.	+530.0	+12.3	−0.4	− 1.0	−0.59	−10.5	+ 1.8	+ 3.0	+17.0	+0.28	+0.5
R. J.	+ 70.0	+ 2.8	+0.9	+ 2.0	−0.22	− 2.8	0.0	0.0	− 2.0	+0.67	+1.1
A. H.	+310.0	+13.5	−0.6	− 1.0	−0.07	− 1.0	+ 1.2	− 3.0	+16.0	+0.92	+1.3
G. B.	+340.0	+13.6	−2.9	− 5.3	−0.18	− 2.3	− 6.9	− 4.2	+10.0	+1.67	+2.2
J. L.	+ 40.0	+ 1.6	−0.3	− 0.7	−0.15	− 2.2	− 0.7	− 2.3	+ 4.0	+0.77	+1.2
Mean	+258.0	+ 9.1	−1.2	− 2.5	−0.26	− 4.1	− 2.1	− 2.3	+11.2	+1.00	+1.52
S. D.	182.0	5.6	1.73	3.81	0.17	3.2	4.53	3.88	8.8	0.54	0.77
S. E.	± 81.0	± 2.5	±0.77	± 1.70	±0.076	± 1.43	± 2.02	± 1.73	± 3.9	±0.24	±0.34
After 50 Gm. of Sodium Bicarbonate in 48 Hours											
W. H.	+610.0	+19.5	−1.9	− 4.5	−0.63	− 9.4	− 8.2	− 6.7	+20.0	+1.50	+2.4
J. P.	+450.0	+12.0	+0.6	+ 1.6	−0.34	− 6.0	+ 5.5	+10.0	+14.0	+1.30	+2.5
R. J.	+390.0	+16.0	+0.6	+ 1.2	−0.49	− 6.6	− 0.7	− 1.6	+20.0	+1.40	+2.2
A. H.	+320.0	+14.0	−1.5	− 2.6	−0.17	− 2.4	− 4.3	0.0	+16.0	+1.29	+1.8
G. B.	+410.0	+16.4	4.8	− 8.6	−1.29	−16.8	−11.7	− 9.0	+21.0	+2.32	+3.1
J. L.	+220.0	+ 8.5	−0.4	− 0.7	−0.33	− 5.5	− 4.7	− 2.9	+11.0	+1.24	+2.0
Mean	+400.0	+14.4	−1.55	− 2.3	−0.54	− 6.9	− 5.7	− 1.7	+17.0	+1.56	+2.33
S. D.	119.0	3.45	1.7	4.0	0.46	5.9	6.66	6.26	8.7	0.8	0.37
S. E.	± 53.2	± 1.54	±0.76	± 1.78	±2.50	± 2.63	± 2.97	± 2.80	± 3.88	±0.36	±0.165
After 40 Gm. of Sodium Chloride in 48 Hours											
W. G.	+470.0	15.1	−9.0	−20.0	..	..	..	..	50.0	3.1	5.2
A. G.	+600.0	20.4	−5.3	−13.2	..	..	..	..	25.0	3.0	5.0
A. C.	+450.0	14.3	−3.8	− 9.3	..	..	..	..	40.0	2.7	4.4
M. B.	+380.0	13.6	−3.0	− 7.5	−0.34	5.2	..	..	10.0	1.3	2.4
P. R.	+310.0	13.7	−5.5	−12.3	−1.19	16.6	..	..	55.0	2.1	3.8
R. S.	+370.0	13.7	−5.5	−10.8	0.00	0.0	..	..	40.0	0.4	0.5
V. V.	+500.0	19.1	−3.2	− 6.4	−0.21	3.0	..	..	0.0	0.6	0.8
Mean	+440.0	15.6	−5.0	−11.3	−0.43	− 6.1	..	..	31.0	1.9	3.16
S. D.	87.0	2.83	1.8	4.3	..	..	..	..	19.0	1.0	1.8
S. E.	± 35.5	± 1.15	±0.75	± 1.78	..	..	..	..	± 7.9	±0.41	±0.73
After 80 Gm. of Sodium Chloride in 48 Hours											
R. C.	+770.0	+25.9	−4.7	−12.2	..	..	..	..	..	1.50	2.3

Thus in Group I at the end of the 2-day period, there was an average increase of 14.4% in the plasma volume, while the average decrease in the hematocrit was only 2.3% and in the serum protein concentration 6.9%. Similar findings were noted in Group II. Changes in the hemoglobin concentration or in the red blood cell count failed to show significant evidence of dilution and there was no significant change in the mean corpuscular volume of the red blood cells.

Discussion. From the results presented here, it is apparent that the addition to the diet of large amounts of sodium bicarbonate or sodium chloride results in significant increases in the plasma volume. Though sodium balance studies were not carried out in these subjects, others[16,20] have reported significant retention of sodium and water following the administration of sodium bicarbonate or sodium chloride to normal subjects. It is, therefore, reasonable to suppose that the consistent increase in weight noted in these subjects was the result of the retention of sodium and water, and represents chiefly an increase in the extracellular fluid portion of the total body water.

Though there was considerable variation between the change in the plasma volume and the change in the body weight after the first day of sodium bicarbonate administration, both groups showed a fairly constant relationship between the change in the plasma volume and the change in body weight, at the end of 48 hours. Excluding Cases R. S. and V. V., the increase in plasma volume in the other 11 cases represented 23.5 ±6.8% of the total gain in the body weight. In Cases R. S. and V. V. the increase in the plasma volume represented 92 and 84% of the gain in body weight. The slightly greater increases in plasma volume and in body weight noted in the cases receiving sodium chloride compared to the groups receiving sodium bicarbonate has little significance in this small series of cases. It should be noted, however, that more sodium was administered with sodium chloride than with sodium bicarbonate, and this alone might predispose to greater changes in body weight. Another factor impossible to evaluate in these cases is the diuretic effect of the alkali, which may in part explain the difference between the groups.

Since sodium retention produced in this manner is related to a significant increase in the plasma volume, it would seem that the plasma volume even of normal subjects cannot be assumed to be constant, but will vary with reasonably small changes in the water content of the body and presumably with the sodium balance of the individual. Krauel[10] has demonstrated a fall in the plasma volume and body weight in normal subjects placed on a salt-poor diet. He also demonstrated that the addition of 10 or 20 gm. of sodium chloride produced an increase in the plasma volume and body weight. Decreases in the water content of the body produced by diuresis with a salt-poor diet and ammonium chloride[11] or by mercupurine[12] in normal subjects is associated with an average fall in the plasma volume of 14 and 16% of the initial determination. Thus it would appear that the plasma volume may be altered by relatively small changes in the body water of normal subjects to as much as 15% above or below the control

determinations. The fact that the plasma volume has been found to be relatively constant in normal subjects is no doubt due to the ability of the body to maintain a fairly constant sodium and water balance when variations in the intake of water and sodium are small.

The increase in the plasma volume following the administration of sodium salts with fluids *ad lib.* suggests that this mechanism might be useful in the restoration of the plasma volume after bleeding, in individuals who may be mildly dehydrated. In general the plasma volume is quickly restored to normal after small losses of blood,[9] but after a blood loss of 15% of the total blood volume, the restoration of plasma volume is said to occur gradually.[3] These studies suggest that the administration of large amounts of sodium salts as a preoperative measure will increase the plasma volume as well as predispose to a favorable water balance. This mechanism might also be of some benefit in operations in which a considerable blood loss could be anticipated, so that the plasma volume would be large at the beginning of the operation.

The failure of the hematocrit, hemoglobin concentration, and red blood cell count to change in proportion to the change in the plasma volume has been noted before[4,11,12,15,18,19] in instances where the plasma volume has been reduced. It is apparent that under these circumstances, the cell elements in the antecubital vein from which the samples were drawn have not undergone the degree of dilution found by the direct determination of the plasma volume. This may be explained by suggestion of Ebert and Stead[4] that there are shifts in the concentration of red blood cells between the smaller and the larger vessels with alterations in the plasma volume. They demonstrated[4] that the cell plasma ratio for minute vessels is lower than in large arteries, veins or bleeding capillaries.

The failure of the serum proteins concentration to change in proportion to the alteration in the plasma volume has been noted before with decreases in the plasma volume.[3,11,12,15,19] A similar situation is apparent in the cases reported here where the decrease in the serum protein concentration is not proportional to the increase in the plasma volume. This may be explained by the theory of Madden and Whipple[14] that the serum proteins are in a state of dynamic equilibrium and may easily enter or leave the blood stream depending upon the stimulus so that the concentration remains relatively stable. These findings, along with those associated with a decrease in plasma volume, suggest that relatively small changes in the plasma volume in the normal subject will alter the amount of circulating protein in the plasma, so that the concentration of the serum protein in the plasma undergoes only small alterations.

The increase in the venous pressure in these cases may be explained either as a result of an increase in the local venous pressure, due to an increase in the tissue pressure, or as a result of an increase in the auricular pressure. Since the veins of the forearm are a series of collapsible tubes, the pressure in them is dependent upon the pressure of the surrounding tissues and the pressure in the right

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auricle. An increase in the amount of extracellular fluid along the course of the vein might cause a rise in the tissue tone sufficient to cause partial obstruction of the vein and thus produce an elevation of the venous pressure. Ryder, Molle, and Ferris[17] have indicated that the peripheral venous pressure is independent of the auricular pressure and is a function of the tissue pressure causing a collapse of the vein along its course to the heart. The variability in the rise in venous pressure noted in these cases suggests that in some instances the factor of local obstruction may play an important rôle. There is no experimental evidence in these cases that an increase in the auricular pressure did occur. However, with a diminution of the plasma volume, there was an associated decrease in the venous pressure and symptoms of a diminished blood flow suggesting a decrease in the auricular pressure.[12] It has been shown that the administration of intravenous fluids is associated with an increase in the cardiac output, especially when there was an increase in the peripheral venous pressure,[1] and it would seem likely that in these cases the increase in the plasma volume may be associated with an increase in the auricular pressure and with an increase in the cardiac output. In any event, the increase in the venous pressure noted in the antecubital vein would be associated with some increase in capillary stasis either local or generalized which would promote greater transudation of fluid from the capillaries into the interstitial tissues.

The considerable variation between the increase in plasma volume and increase in body weight noted after the first 24 hours on sodium bicarbonate compared to the more constant relationship in 48 hours suggests that the equilibrium between the plasma volume and extracellular fluid disturbed by the addition of salt and water had not been reëstablished in 24 hours. It would seem reasonable to expect that as salt and water are absorbed from the gastro-intestinal tract the plasma volume is slightly increased. This gain in plasma volume may be at first quickly lost to the extracellular fluid spaces. With increases in the amount of fluid in the interstitial spaces the tissue pressure will be increased and will result in a decrease in the amount of fluid leaving the capillaries. At the same time, protein is added to the blood so that the osmotic pressure in the capillary does not significantly fall as a result of hemodilution, and the plasma volume may thus be maintained. If such a hypothesis be true, it should be expected that considerable variations would be found in normal subjects depending on the rate of absorption of water and salt, the rate of excretion, the volume of extracellular fluid, the tissue pressure, the capillary pressure, and the serum protein concentration.

Summary. 1. A significant increase in the plasma volume was noted in 14 subjects receiving large amounts of sodium chloride or sodium bicarbonate.

2. The increase in the plasma volume was accompanied by an increase in the venous pressure and the body weight, but was not accompanied by a proportional fall in the concentration of serum protein, hematocrit, hemoglobin concentration, or red blood cell count.

3. Six subjects receiving 50 gm. of sodium bicarbonate in 48 hours had a mean increase in plasma volume of +400 cc., ±53.2, or 14.4 ±1.54%, with mean increase of body weight of 1.56, ±0.358 kg., or ±2.33 ±0.165%.

4. Seven subjects receiving 40 gm. of sodium chloride in 48 hours had a mean change in plasma volume of +440 ±35.5 cc., or +15.6 ±1.15%, and a mean increase of body weight of 1.9 ±0.41 kg., or 3.16 ±0.73%.

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ORIENTATION OF THE ARMY PSYCHIATRIST

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The psychiatrist, probably more than the practitioner in any branch of medicine, is his own diagnostic and therapeutic instrument. Where the syphilologist has a laboratory, the radiologist an objective shadowgram of the particular bodily region which absorbs his interest, and even the internist a thermometer and the testimony of his auscultatory finger, the psychiatrist dealing with those functional disorders peculiar to his field must rely exclusively upon his understanding, his memory and his judgment: understanding of human nature, of his patient's personality and of his particular problem; memory of other cases with their marked differences and subtle similarities; judgment to classify without doing his patient undue violence, to advise discreetly and to treat within the limits of anticipated benefit.

Experience has forged the general practitioner a yardstick which in a general way can be applied to medical disorders with positive diag-

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nostic results. The index is flexible and must expand and contract within certain limits to include the atypical and the aberrant; but it is a poor physician who mistakes scarlet fever for a fractured femur and by no means an inept psychiatrist who mistakes a manic-depressive psychosis for schizophrenia. The internist could satisfactorily state whether or not a Martian was suffering from tuberculosis but the psychiatrist would be quite unable to decide whether he was psychotic, a genius, or an average extra-terrestrial specimen. In his own field the psychiatrist must get along without firm well-established clinical syndromes and must daily perform the paradoxical task of diagnosing and treating disorders of a perpetually unique nature. Psychiatric diagnosis is accordingly a subjective affair and the formal classification of any patient only a sort of makeshift which has no importance to the physician already familiar with the case, and only a limited value to his successor.

The only dichotomy between "Mind" and "Body" is happily an issue no longer. The competent internist, along with the specialist in the non-psychiatric branches of medicine, realize that it is impossible to treat a disease and ignore the patient; that taxes, marital disharmony and wayward children do have a bearing on John Doe's peptic ulcer. Yet for the proper diagnosis and management of our patients the new monism cannot be carried to absurd lengths. It is still fair to say that pneumonia has more connection with the pneumococcus than with the patient's distress over an early alopecia, and at the opposite extreme that the obsessive-compulsive states relate more to constitutional, environmental and conditioning factors than to microörganisms. The medically "ill person" is apt to be a more or less healthy "person" afflicted with a more or less serious "illness." In the psychiatric invalid the accent is reversed. His "person" is ill and his symptom manifestations are but the disruptive reverberation of this central canker. Try as we will we may be unable to find that an attack of chickenpox has had any relationship to our patient's personality, but we are not obliged to believe that a psychoneurosis has its prodromal, clinical and convalescent stages, leaving the same old "normal self" with a few added scars.

Measles and carcinoma of the breast bear more resemblance than measles and schizophrenia, in the same sense that one recognizes oranges and apples as more akin than oranges and justice. To approach psychiatric disorders with a "yardstick" of symptoms and signs, to hope that a "Wassermann test" for hebephrenia will eventually come out of our research laboratories, to visualize an exogenous disease process descending upon the organism in the way that typhoid fever invades its victim, is to plunge unprofitably against a permanent and sterile impasse. One does not attempt to adjust a mine-workers' strike with a kit of mechanic's tools nor does one grind the valves of an internal combustion engine with Emerson's Essays.

The medically oriented physician is told by the psychiatrist that he must consider the intangible elements in his cases, yet he may not be informed that his familiar tools, his diagnostic and therapeutic tech-

niques and perhaps most importantly of all his very habits of thought must be discarded and a radically divergent approach adopted. Psychiatry is not an exact science, nor is politics, nor philosophy. What does one weigh? What does one measure? Modern clinical medicine, although few would include it in the relatively exact disciplines of physics and chemistry and certainly not in the completely "scientific" field of mathematics, still employs genuinely scientific techniques which have resulted in the brilliant advances of the past few hundred years. Psychiatry, when dealing with those disorders preëminently its own, has signally failed whenever it has attempted to employ the same approach. Psychiatry's spiritual father is Aeschylus and not Hippocrates, and its practitioners have more to learn from Phidias, Shakespeare, El Greco and Milton than from Sir William Osler.

Therapeutics, *per se*, is intimately related to the practitioner's understanding of his individual patient and in the reversible disorder, productive or ineffective in direct proportion to the physician's grasp. The psychiatrist must, therefore, be at all times keenly aware of his own "tare" which will inevitably and radically vary, depending on the type of practice he is doing and upon the circumstances of his own existence both environmental and subjective. His experience, actual and vicarious, must be of an extent and diversity to permit him a common ground with every patient who comes under his care. As this common ground narrows, his ability to diagnose and to treat recedes and may eventually reach a hypothetical point of non-existence. It is a dim realization of the validity of this by the relative and lay friend that leads him so often to insist that he "knows" the patient "inside out" and so can do far more therapeutically than the psychiatrist. The basic premise is sound but the application is in error since this "knowledge" is usually more of the patient's effect upon him than of the patient. Furthermore, the ability to use even what objective knowledge exists is stultified by his personal ties.

It is the psychiatrist's constant effort to understand rather than to sympathize, to be objective rather than partisan, and at the same time to know his own prejudices, aims and fidelities and when they minimize one facet of his patient's personality and exaggerate another to make the necessary correction in his conclusions. A form of identification takes place with the sufferer, a projection into his being. He strives to react with another's instincts, feel with his emotions, think with his mind, all in an attempt to strike closer to the knowable truth concerning him. Not the metric truth of cubits in his stature, not the subjective truth of chiming music in his voice, but rather the transcendental truth of Who He Is.

Remote as these comments may seem from the practice of Army psychiatry I shall endeavor to demonstrate their relationship.

The civilian psychiatrist will usually be found in institutional work, penal consultation, private practice or the psychiatric out-patient clinic of a University or Foundation. In the State Institution the patient census is made up of individuals deriving from a relatively narrow geographic area. In a general way their economic situation is

similar. By and large they are all psychotic. In practically every instance their illness has been of sufficient severity to attract social notice culminating in their commitment.

In penal work individuals coming to the psychiatrist's attention are even more rigidly "selected." All, if not actual criminals, have at least been accused and convicted of anti-social acts. All face an essentially identical environmental situation: enforced confinement and social stigma.

The private psychiatrist, perhaps most of all, sees a sharply differentiated group of patients. His work will be done within certain economic brackets, the majority of his cases will share with each other either an awareness of their illness and a desire for help, or will have families who recognize these issues more or less completely. He will continue to treat only those who feel they are profiting by his assistance or whose families hold this opinion.

The physician working in a private sanitarium, in an out-patient clinic, in a teaching Institute will in turn find that his practice has a certain year in, year out uniformity that in itself facilitates the discharge of his responsibilities.

In general, then, one may say that the civilian psychiatrist in whatever field he may be working, deals with a highly *selective* group of patients who share with one another many important similarities and who either recognize the fact of their illness or have others (the family or society) who do so for them. The psychiatrist can in consequence approach a case with a background of familiarity, the very existence of which he may not recognize. He is usually aware of the mores which have impinged upon his patient because they have also influenced the physician. He knows automatically from the patient's address in what climatic conditions he has been living. It is not improbable that he may know the patient's employer or the reputation of the business house of which he happens to be the head. His dress tells as much about his personality as it does about his pocketbook.

In military practice the geographic, economic and social background of the patients is heterogeneous to a degree that has no civilian counterpart. Every State in the Union is represented, every financial situation, every intellectual endowment, every cultural level. The millionaire wears the same shade of olive drab as the pauper. The genius salutes with the same gesture as the mental defective. The Maine woodsman inflects his "Sir" in the same fashion as the California hotel manager. He comes under the observation of the medical officer for one reason only, failure to be a satisfactory soldier. He may, of course, be ill and often is, but the line officer and the first sergeant are not functioning as health advisers. They naturally and correctly evaluate the enlisted man as to his military possibilities. How able a salesman may be, how satisfactorily a coal miner has met his civilian problems, what magnificent books an author has written, are no longer pertinent. Can he fight? Is he of any use in one of the services of supply? Men who are not "good soldiers" include a great many human types with whom the psychiatrist has had no previous contact and yet

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in a great many instances it is just these men that, in course of time, he is asked to evaluate.

The civilian psychiatrist has *ipso facto evidence of the patient's illness* in the average professional situation, for otherwise no provision would have been made for his examination. To him, "What illness afflicts this individual?" is a rather different question than "Does this patient have any type of disorder?" Only in the field of industrial medicine where compensation and liability necessarily bulk large is he asked the second question as often as in the Army.

To the civilian population of the United States and correspondingly to its medical practitioners Peace is thoroughly comprehensible; War, strange, European, and largely inexplicable. It is far easier to understand the plumbing business, the stock market, library schools and Ringling Bros. Circus than it is close order drill. Although Americans have fought considerably more than the continental average of a war a generation they have remained singularly untouched by militarism in any of its manifestations, concrete or ideologic. Even such a simple military prerequisite as conscription had to be elaborately disguised and fitted with a euphemistic title that appealed to peace-time fetishes. The deep-sea diver, and the lumberjack talked a language in 1941 far more comprehensible to the psychiatrist than can be spoken by any sergeant to his recently commissioned medical officer. The psychiatrist newly in uniform not only has no understanding of *the War Situation* in which his patients find themselves, but, since his duties confine him to the purlieus of the hospital, has little means of finding out. What do the men talk about when no officers are present? What is the actual effect of disciplinary action on group morale? Just how "tough" is a sergeant? What does Private John Doe really think about the war, about giving up his job, about relinquishing what he has always thought was personal control of his own destiny? What is the "average" soldier like? These and many other questions he is obliged to ask himself, for it is only through his ability to answer them accurately that he can fulfill his professional function.

A no less challenging task before the psychiatrist lies in familiarizing himself with the *Aims of the Army*. What constitutes disability in the psychiatric field? What is the minimum standard of the individual soldier's performance which makes him an asset rather than a liability to the armed forces? The answers to these and kindred queries are not as simple as might at first appear. Man has sought throughout the ages for codification, believing perhaps naively and perhaps not, that through carefully worded regulations and the establishment of standardized procedures, recurrent situations could be dealt with in a uniform and just manner. Moses' Ten Commandments, the Roman Law and the Napoleonic Code were such attempts. Army regulations and the Articles of War are others. Admirable as these guides are, they do not, nor can any such body of regulations hope to avoid interpretation or the inescapable fact that they will be administered by human beings in connection with human situations. It is possible so to interpret AR 615-360, Sect. VIII that any individual in

whom signs of viability are present and who is able to make a purposive movement such as lifting an arm must "by regulation" be retained in the Army, even though he be an overt homosexual, a morphine addict and have a mental age of 3 years. It is also possible so to interpret this regulation that an infantryman afflicted with a degree of native awkwardness greater than that shown by his fellows but with the sterling qualities of a Sergeant York must "by regulation" be dismissed from the service. The psychiatrist must learn where along this interpretive scale are the limits of actual practice at his particular post and in his particular organization, for although the regulations throughout the Army are uniform, it is no secret that a "Section VIII Discharge" may be "easier" under Colonel B. in Maine than under Colonel A. in Texas.

Education constitutes the last category for discussion. The civilian psychiatrist in every professional situation in which he may find himself, with the exception of a certain type of forensic practice, is dealing either with other psychiatrists (the Psychiatric Institute's seminar; the State Hospital conference) or with medical practitioners who have sought his advice and who accordingly are quite ready to accept his judgment and interpretation. In the military field the final decision regarding his cases frequently rests with a board of medical officers entirely untrained in psychiatry, whose efforts to fit the needs of an individual problem to the printed regulations may not invariably be in accord with Army aims. With the authority of such a board to pass on what standard of performance is requisite in the individual soldier for military service there can, of course, be no argument, but it is both the privilege and the duty of the psychiatrist to make certain that the members of the board are fully informed of his patient's status and of the "life history" of the disorder with which he is afflicted. He is handicapped by having no roentgenograms with which to demonstrate the disability, no objective physical signs which all can test for themselves, so that there is no particular occasion for surprise when a non-psychiatrically oriented board hesitates over the discharge of a psychoneurotic of perfect physique and superior intelligence.

Once the psychiatrist's standards are brought into conformity with Army Aims, once he has become "psychiatrist to the American soldier" and can interpret and understand the Tennessee mountaineer equally with the Detroit shop worker and the Vermont farmer, once he has learned to differentiate between an illness and a case of guard-house boredom, once he knows what the war situation means, first to himself and then to his patient both environmentally and subjectively, he is in a position to help his professional confrères to an appropriate course in handling his patient's problem.

The following cases are offered for consideration, illustrating in a concrete way, it is hoped, certain of the issues raised above. The first is close to being a man from Mars and demonstrates the difficulty of psychiatric evaluation when the racial and cultural background of a patient is unfamiliar to the examiner. It is problematic whether any

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but a New Englander could thoroughly understand the second man and doubtful that either he or the third case would have come to the attention of a civilian psychiatrist. The traditions, personalities, symptom-complexes, motivations and maladjustments of all are unique and their respective diagnoses distinctly subjective and legitimately open to question. None had any objective physical illness, none showed abnormality on laboratory studies and none was functioning in a healthy fashion.

Case 1. A.B. was a Japanese prisoner of war admitted to the Hospital after 10 months in the Enemy Alien Stockade. A number of his fellows insisted he was insane, while others declared he had only incurred the dislike of a certain clique among the prisoners by his independent ways. Officers in charge of the Stockade reported him as being uncoöperative and resistive to discipline. On several occasions he had been seen by Army personnel openly masturbating and once was said to have completed the procedure in the midst of several waiting soldiers, finally turning to them and blandly asking their business with him. An opinion regarding his mental health was desired.

The patient was a short, wiry Japanese of 41, pleasant in manner and cooperative to hospital regulations. He preferred to remain bare-footed and when seated in a chair would draw up his knees until his feet rested against his thighs. He moved with the quickness and agility of an acrobat, and his gait invariably held something of a swagger, borne out by the habitual expression of tolerant superiority and amused indulgence with which he spoke to the examiner. The most striking thing in his appearance was a full black beard which he wore with obvious pride. His grasp of English was rudimentary and it was with the utmost difficulty that any verbal interchange could be effected.

He had been born in Japan, November 1, 1902, the third of 5 children. One sister had died at 10 of influenza. He had heard nothing of the remaining siblings since their immigration to Brazil 10 years previously. His father, a farmer and a keeper of the Shinto shrine in his village, had died at 65 of heart disease and his mother at 61 of "kidney trouble." Familial diseases were denied. The patient disclaimed neurotic traits, illnesses, serious injuries and operations, declaring, "Since I am born I never been sick. Always strong. Healthy family." It was apparent that he took much satisfaction in his robustness. He had started school at 7 and had stopped at 16 completing the 8th form in a Japanese public school. He claimed to have always had a high scholastic average and to have gotten along well with his contemporaries and instructors. He held class offices in school and was active in athletics, particularly track and swimming. He was not interested in furthering his education beyond the minimum required by law, having made up his mind at an early age to travel.

For 4 years after leaving school he worked on his father's farm, a property of 50 acres, said to be an average size for his country. At 20 he moved to Tokio where he lived with his step-brother, a wholesale merchant in an especially fine grade of silk woven in the patient's own village. During the days he assisted in his step-brother's store and at night attended school where he learned his first English. At 22 he came to the United States and lived in and about New York City until December 1941 when he was taken into custody as an Enemy Alien. In the United States he operated concessions at amusement resorts and claimed to have owned several wholesale and retail businesses dealing in Japanese merchandise. His average income was between $40 and $50 a week. He drank and smoked in moderation but denied the use of drugs. He stated he had resorted to prostitutes once or twice a month until the age of 30, but with the subsequent decrease in his sexual urges had felt little interest in coitus. He had never been married or engaged, declaring there was "too much trouble" associated with the marital state. He gave his religion as Shinto and stated that he observed its tenets faithfully.

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The patient stated that movies, reading, and watching athletic events were his chief interests and spoke of going occasionally to Coney Island or Long Beach to swim. Some 10 years previously he had abruptly severed all social contacts except with his immediate relatives declaring: "I like peaceful living, quiet. Thinking. Study time. So I didn't make friends. I know many people but not close you understand. All simple." He denied that anything happened at this time to influence his decision. "Just my own desire you know." He further stated that 3 years previously he had severed all correspondence with a step-brother living in Stamford, Conn., by common consent, since they did not want to have "trouble." No clarification of what constituted "trouble" was possible except the patient's puzzling idea that all human contacts in the United States were dangerous because there was no "righteousness" and too much "competition." He had no hobbies, belonged to no societies or clubs and cultivated no cultural interests. He had never been arrested.

One of the officers from the Stockade reported that the patient had been difficult to manage from the time of his arrival and had never considered himself bound either by military discipline or the regulations set up by the Japanese internees. He bullied his tent mates and spent much of his time striding about the area smoking a pipe and swinging a cane. The other prisoners were said to avoid him as much as possible. Many of them were afraid of him and some regarded him as mentally unbalanced. At mess call he would frequently continue his promenade and, after the other men had been fed, demand something to eat for himself. Gossip among the Japanese was to the effect that he had at one time been a patient in a mental hospital in New York or Massachusetts. They also believed he had adopted his present name several years previously when he became estranged from his relatives because of his irresponsible conduct, shiftless ways and frequent intoxication.

In hospital most of his answers to questions were circumstantial and seemingly tangential. In reply to almost every query he brought in some mention of his religion and philosophy. He flatly denied open masturbation as reported by the officers, stated he got along well with the other men and denied that he had ever been in a mental institution. He did not regard the Japanese spokesman at the Stockade as a suitable choice since he was a Christian convert and a missionary, and accordingly could not properly represent those of his race who were of other faiths. He admitted that he did not consider himself bound by any decisions made for the group by this leader. He professed to be on excellent terms with what relatives were living in the United States and declared he never became drunk oftener than once a year and then only for a short period.

He was eager to point out the defects of Western civilization and to praise Japan's cultural advantages. He talked at length about Shintoism and its basic concept of Righteousness, from which stem Humanity, Freedom and Liberty. In some way not clear to the examiner he justified his friendlessness and isolation on the absence of a patriarchal social organization in the United States. The natural order, he maintained, was for the family and all society to be hierarchial, with the male dominant, the female under his jurisdiction and children at the lowest stage. This was proved, he contended, by the fact that the sun is male, the moon female and the stars immature children. Some 10 years ago he awakened to the dangers and potential "troubles" of friendship and subsequently isolated himself as completely as possible from his fellows, maintaining only "simple" (casual?) relations with them. He declared with a great deal of pride that he was a "student," and had thoroughly examined Western civilization with especial reference to its religion and its politics. He liked "a quiet life" in which his meditations were not disturbed and became almost ecstatic in describing its merits. He regarded his hospitalization as a "double cross" initiated by a small Japanese clique among the prisoners who did not regard him highly and who had succeeded in duping the Army personnel into a belief that he was "sick." He was certain there was no rational motive for this, declaring it was only because these men were "nervous"

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(insane). The patient's sensorium was entirely clear, his mood was undisturbed, it was not possible to elicit hallucinations and his intelligence appeared to be adequate although probably no more than dull normal.

Cultural and racial differences, the language barrier and the effect of war attitudes on the patient's candor raised insoluble difficulties in formulating his disorder. Was he only an eccentric and lonely man of modest endowment reacting to a hostile and incomprehensible physical and spiritual environment by a schizoid retreat and the glorification of a self-created philosophy and half-fabricated religion which he identified with his home land? Was he a wastrel and an outcast, a rowdy vagrant? Was he, in reality, a schizophrenic whose overt symptomatology appeared 10 years previously when he retreated from society, fell out with his relatives, and became economically ineffectual? Was he, in his present situation, dramatically manifesting further dilapidation in conduct by his open masturbation? It was readily ascertained that he did not have syphilis, that he was not suffering from pulmonary tuberculosis, that he was not a victim of diabetes. No finely calibrated scale was at hand to determine whether or not he was insane.

CASE 2. C.D. was a native of Vermont who had been in the Army for 5 months. He was referred to the Hospital because of stomach trouble which had been particularly troublesome within the past year and which he stated was relieved at times by taking food and at times by passing flatus. He was originally admitted on a medical ward. Gastric analysis was normal and he displayed no secondary anemia. A barium enema showed no evidence of colitis or other pathology in the large bowel and his feces were negative for occult blood. Cysts and pre-cysts of *Endamœba coli* were repeatedly found but were not thought to have an etiologic bearing on his complaint. Twelve days after admission he was seen by a psychiatric consultant. He spoke of being "nervous" for a long time, but was unable to date the onset more accurately. He stated he was easily excited, was often "shaky," suffered from palpitation and described prickling sensations in his arms and "funny feelings all over" for which he could not account. He admitted that he was "kind of depressed at times" and that he seemed constantly on the verge of weeping. He had been unable to sleep well during his period of military service because of the noise from card players and from intoxicated soldiers coming into the barracks late at night. He was transferred to a psychiatric ward the same day.

The patient was 37 years of age, of medium build and of a courteous and retiring manner. Throughout his subsequent hospitalization he spent much of his time alone in his room, at times reading and at times in idleness. He volunteered no complaints, rarely spoke to the other patients and showed no interest in the activities of the ward. His facial expression was sober rather than depressed, he showed no signs of retardation and his apparent preoccupation was never of a degree to impair his awareness of his surroundings. He readily carried out whatever housekeeping tasks were assigned him and replied pertinently and without hesitation to questions addressed him.

He had been born in Vermont, November 2, 1906, the third of 4 children. One brother died at 36 after 25 years in a mental institution probably for an epileptic psychosis. The 2 remaining brothers were living and well. His father, although still alive at 72 was in delicate health and his 70 year old mother suffered from "nervous trouble." Familial diseases were denied except for 2 instances of fatal tuberculosis. He was uninformed regarding his birth and early development but stated that temper tantrums had been common in his childhood and that he had never outgrown the habit of biting his nails. Other neurotic traits were disclaimed. He had suffered from all the minor exanthemata and at 10 had undergone an attack of scarlet fever without apparent residuals. A tonsil and adenoidectomy was performed at 27 and a herniotomy and appendectomy at 33. At 21 or 22 he had acquired gonorrhea which was followed by an arthritic involvement of the left knee. This continued to cause him pain after any unusual exercise. Other serious illnesses and operations as well as injuries of significance were denied.

He had completed public high school at 18 with a scholastic average of

"C." There had been occasional truancy, but in general his deportment had been good. He had gotten along with both instructors and classmates without trouble, but had mixed little with the other students and had never been a popular boy. He had participated in none of the extra-curricular school activities, belonged to no societies, taken no part in athletics and had never held a class office. Although his family would not have objected had he wished to enter college, he had shown no interest in furthering his education.

After leaving high school he worked for the following 4 years as a marble cutter, fashioning cemetery stones. For a time his salary was $70 a week. At 21 he and 3 companions were making a purchase of some beer from the local bootlegger when an argument arose over their having been short-changed. One of the patient's companions struck the bootlegger with his fist, discoloring his eye. The man brought charges against all 4 and the patient and 2 of his companions were sentenced to 9 to 12 months in the penitentiary. The patient was released after 8 months, immediately gave up both alcohol and tobacco to which he never subsequently resorted and changed his employment from stone cutter to handy man in the kitchen of a Fine Arts College in his home town. He remained for the following 15 years in the same employment at a salary of $25 a week. After several years he was made assistant cook. He would visit at home several times a week and would occasionally stay overnight with his family, but actually made his home at the College where he lived with 4 to 6 other employees, pastry and meat cooks, dish washers and kitchen men. Throughout this period he never went out socially with any of his fellow workers, never participated in the activities of the common room which they all shared, and consistently kept to himself.

His alcoholic indulgences, which for a time reached a maximum of one pint of spirits in the 24 hour period, were confined to his young manhood, the patient drinking nothing before he was 18 and nothing after his release from prison at 22. Tobacco was abruptly discontinued at the same time. "My stomach and nerves couldn't stand it," he explained.

The patient's family were Congregational by faith and quite devout in their observances. The patient had never been interested in formal religious issues but considered himself a Christian man. He had never married or been engaged and admitted that even casual social contacts with members of the opposite sex were infrequent. He had never resorted to prostitutes, had never fallen in love and could even recall the approximate number of sexual contacts in which he had participated during his lifetime. Homosexual experiences were denied. Concerning masturbation he stated that "of course it would injure your health and run you down." He felt it "couldn't help but weaken the mind." Although evasively denying that he had observed any such harmful effects upon himself and disclaiming any fears that he might go insane as the result of the practice, it was evident that he had given the matter considerable thought.

His amusements had consisted of attendance at the movies 2 or 3 times a week, of hunting and fishing, of reading the newspapers and of listening to the radio. His hunting was done alone because "there wasn't so much noise," he rarely "bothered" to go with any one to the theater and it was naturally more convenient to read and to listen to the radio in the privacy of his room. He had no hobbies and no cultural interests. On his visits at home he almost never came in contact with anyone but his immediate relatives since they "didn't go out much or have people in." He had been arrested but twice: once at the age of 20 for drunkenness and again at 21 for disturbing the peace. It was following conviction for this offense that he spent 8 months in the penitentiary. In the Army he had been subjected to no disciplinary action and had never before been hospitalized. He had reported on sick calls some 4 or 5 times in all, invariably complaining of his stomach.

The patient was unable accurately to fix the date of onset for his complaints of "stomach trouble," dyspnea, precordial distress, tension, epigastric burning and "nervousness" but stated they first became noticeable in early manhood. In search of relief he gave up both tobacco and alcohol at 22 but continued to

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be intermittently troubled in the following years. In 1942 his symptoms grew so annoying that he consulted a physician who, after a thorough examination, declared they were the result of "nervousness" rather than of any organic pathology. Military service, so greatly out of keeping with his customary life pattern, aggravated his complaints. He was unusually distressed by the noise and bustle of camp life, the propinquity of other soldiers and the rapid pace of events. He became depressed and episodes of tearfulness were common. His outstanding complaint on admission to hospital was of gastric distress, and initial examination procedures were conducted on an appropriate medical ward. They failed in every instance to demonstrate an objective basis for his trouble. The patient displayed no disorder of speech, no projectional delusions and no hallucinations. His sensorium was normal and his basal intellectual faculties intact and adequate.

Could the abrupt relinquishment of a profitable trade, the apparent contentment in a poorly remunerated, semi-domestic job, the sudden renouncement of the sins of tobacco and alcohol have been the profound reaction of a conscientious and penitent youngster to an adolescent misdemeanor which society had punished by a harsh penitentiary sentence? Were the inflexible rigidity of his past life, the paucity of his interests, the habitual seclusiveness of his existence but a literal application of New England traditionalism, personal restraint, and conventionality? Was he a neurotically insecure, poorly adjusted and distinctly schizoid personality hiding from the stresses of human contact in the basement of a College dormitory, perverting his instincts, disrupting his personality and sinking continually deeper into hypochondriacal dilapidation? Had his native store of initiative, of energy, of interest, burned itself out before he was 22, leaving him an emotionally empty and purposeless derelict who maintained the illusion of human, although somewhat eccentric behavior until he was taken out of his habit-bastioned environment and thrown into the parlous uncertainties of an Army camp? Was he a Saint, a New Englander, a Psychoneurotic, a Schizophrenic, or was he C. D. the unique creation of an endlessly inventive Providence?

Case 3. E.F. was born in New York City, and first entered a military hospital after 9 months of service. The psychiatric out-patient report authorizing his admission read as follows: "Profound depression. Marked feelings of depersonalization. A great deal of content is schizoid. Admit to closed ward." His commanding officer stated that he had found the patient intelligent but unadaptable, that his only interest was in textiles, and that he was "completely useless" in his present assignment in the Infantry. Every effort made by his organization to effect his transfer to the Quartermaster Corps had been unsuccessful and it had been decided to refer him to the Hospital in the hope that he could be reclassified. The patient insisted that in his attempt to persuade the medical officer of the need for his transfer he had overstepped himself and convinced him rather that he was mentally ill.

The patient was a man of large but unathletic physique, coöperative, suave, and volubly eager to make clear his situation and to correct the physicians' erroneous notion that he was psychotic. He mixed little with the other patients and spent much of his time reading and carrying on a voluminous correspondence. He immediately began to ask for unusual privileges, particularly the use of the telephone, and at no time let it be thought that he considered himself one of the ward patients. He was on terms of easy condescension with the attendants, showed a polite reserve toward the nurses and was respectful but faintly impatient with the medical officers. He collaborated with them on his "case," exchanged suggestions, and permitted himself no doubts that all concerned were of one mind as to the proper thing to be done. Ascertaining on his first day in hospital that all outgoing mail was read by the doctor before it was posted, he instituted a campaign which made up in volume for what it lacked in subtlety. He discussed his situation *in extenso* with a half dozen correspondents and when no more remained, began to cycle again, interminably repeating himself even as to the phraseology in his numerous letters. His speech was rapid, emotionally surcharged and for the most part overpower-

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ingly plausible, an odd, elliptical, short-hand utterance with many elisions and apparent indirections which he was, nevertheless, always able to clarify on request. When well launched on some recital, he seemed to become hypnotized by the sound of his voice and raised issues and made revelations which were not altogether consistent with the impression he attempted to make at other times.

He had been born on July 28, 1905, the first of 3 children. Two brothers were living and in good health but his father had died in 1920 of heart disease at the age of 45. He had been a "converter of cotton goods" and it was from him that the patient first became interested in the textile industry. His mother, living and well at 58, had remarried in 1927 but had borne no children to her second husband. Familial diseases were emphatically denied. The patient scouted the suggestion of childhood neurotic traits, at times offering a vigorous negative before he had actually heard the examiner's question. "I am very calm, serene, even temper. Always been that way. Never ruffled. I am a healthy person," he declared. "Go through my record from A to Z. Friends, business associates." In similar fashion he disclaimed all of the exanthemata, all injuries, all operations and all serious adult illnesses, although as an afterthought he did admit to a tonsil and adenoidectomy.

He attended school until the age of 22, completing a 3 year course in textile school. During the latter part of his academic career he attended evening courses in a school of business administration in a reputable eastern university. He gave his scholastic average as "80," and insisted that he liked school "very much," played baseball both in high school and college and for a year and a half sat on a student government board. "I was just one of the boys," he stated, "I am always one of the boys. Fellow my age, though, you can't feel intimate with fellows 21, 23, 24. You feel interested in them but you can't feel too close. At least that's the way I feel. I do the best I can. I mingle with them in the barracks but I wouldn't go out of the way for some of the people I met. It's the Army, the great melting pot." He went on to contrast his school day companions: "They were all my kind. Easier to talk to and be with. Mutual interests." He admitted to rare truancy but added, "I guess that's normal," a statement which prefaced much of what he said. He failed his Regents examinations on the first attempt but qualified the following year.

The patient obtained work in a textile corporation as a "styler and fabricater" immediately after graduation. In the following 15 years he held jobs varying in duration from 2 to 4½ years with 5 different concerns, all of them textile industries. With the last 2 firms he was head buyer. In each instance he maintained that his change of employment had been by resignation and had represented an advancement either in responsibility or from a financial standpoint. He repeatedly mentioned how distressed his various employers had been at losing his services to another and at times rival organization. His income had been large and on at least 5 occasions he informed the physician that he had allotted his entire Army pay to the purchase of War Bonds. He employed tobacco and alcohol in great moderation and denied the use of drugs.

Although unmarried he was "practically engaged" to a divorcee of 37 whom he had known for the preceding 8 months. Explaining his delay in marrying he stated: "You get spoiled by too many good times, by the fine association you have with many people. You realize when you are older the mistakes you make when you are younger. I should have married while I was in college. Nice girl, but I guess I was just a little too fickle. The time just went by. My brothers are already married and have children and they are younger than me. I am still just floating around."

He spoke with romantic hesitation of a former sweetheart with whom he went for 2 years and who represented all that was femininely desirable. She, however, was a Catholic and although he arranged for her to take instruction from a Rabbi, eventually was unable to overcome his religious scruples and marry her. His one visit to a prostitute had resulted in an unsatisfactory contact, the patient being unable to obtain an erection. He had also experienced a relative degree of libidinous blocking with girl friends but never to this degree, and presented a distinctly feminine disinclination to coitus unas-

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sociated with idealistic identification. "When you try to satisfy lust mechanically it isn't genuine passion. I have had no intercourse now since New Year's and it isn't anything. I have too multifarious interests whereas if you are with these young fellows it's their only interest." He denied worries over masturbation declaring: "It was never my concern. Never worried about it, never practiced it. I guess I know what it means" (laughing).

The patient's family were strictly Orthodox but he was even more rigid in his observations. He never worked on Saturday and made a point of getting home before sundown on Friday night. He followed the dietary laws and stated that he had eaten no meat since his induction 9 months previously. "The only thing I hate about this thing is I haven't been able to put on strips for the morning prayer," he declared. He had worked with a private tutor in childhood instead of attending Chedar and had continued to study with learned Hebrews until the time of his induction. He had held the office of President of a New York temple and had been a member of the administrative board of a national Jewish religious organization for 5 years.

He had always lived at home and stated that he got along well with his mother and step-father. He liked golf, the theater, dancing and "other normal pastimes"; ice skating, tennis and skiing, "all these things that we all like to do. I like cruises in the winter time. Miami in the winter time. The normal things." He claimed to read a great deal, preferring "something with depth; I don't like just plain fiction, autobiography, something with depth." He professed to collect books, although he actually bought them only for their contents. He had played the piano as a younger man but had found "no opportunity since college days."

He denied that he was or ever had been ill, maintaining that his whole problem centered upon his placement in the Army. He felt that he had never been in a branch of service in which his own particular talents could find expression and although expressing his willingness to serve wherever he might be assigned, hedged his statement by the declaration that he could not "become interested" in anything but textiles, and that a number of officers had told him he should be in the Quartermaster Corps. He had appeared before an Officers Candidate Board shortly after his arrival at the Post requesting assignment to a Quartermaster school but was rejected. His commanding officer, he stated, had made every effort to transfer him out of the Infantry realizing that he was "no soldier," and when all else failed had decided to attempt his reclassification. He had been sent to the Psychiatric Clinic with a tentative diagnosis of "neurosis" but declared he "made the mistake of putting it on too thick." He told the doctor he felt aimless, blank and hollow inside, that he was listless and that one half of him didn't know what the other half was doing. His days were "lifeless," they "weighed upon" him, and even over the week ends when he was away from camp he felt depressed and dissatisfied, brooding constantly upon his unfortunate situation. "The thought was lurking in the back of my mind even in the midst of my friends and all the confusion of this much-ado-over-nothing existence. Just filling up time." When the psychiatrist had asked him regarding suicidal notions he told him he was "betwixt and between," by which he meant that he had made no overt attempt but had frequently thought of the possibility. "In other words, my words indicted me, that's the answer I guess. I put it on too thick with the Major and he sent me to the ward."

Finding himself among psychiatric patients and being intelligent enough to realize that this inferred a great deal more than simple reclassification the patient conscientiously attempted to minimize his original statements and give an overwhelming impression of robust normalcy and hearty good health. He telephoned friends and acquaintances 1 to 3 times a day and kept up a great stream of correspondence in which he adopted a satirical approach to his hospitalization, assuring his friends that they "would surely get a laugh" out of his self-created predicament. Extracts from his letters are given below:

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MONDAY AFTERNOON
"Start laughing" (watch taken away from me)

DEAR B.

Fortunately those characteristics which have been inherently imbedded in me now supply their succor and healing unto me. Placidity of disposition, a happy mien, plenty of reserve, etc. act as a solace—call it a time palliative for this unnatural life which is presently mine. Believe me—it sure strikes me funny for the while—but I'd sure loathe the idea of being confined here indefinitely. You take a healthy normal being and mix him in with some neurotics and such—peculiar changes might occur to even alter my stable being. It's interesting for a few days to dwell in such a house. Thusly—I am enabled to obtain some perspective as to the feelings—moods engendered by others who must seek their shelter here.

Reverting to how I landed here, it is certainly a case for the "Books" and I mean "The Strange Case of E. F." As you well know, my Captain realizing that my potentialities in an infantry way are nil—proposed that I be re-classified. The Captain (doctor) at the dispensary—in order to state some cause for re-classification suggested "neurotic condition." He advised me as to how I should state my case to the Major. The result of this interview, especially with reference to the wordy content on my part (I put it on too thick) landed me in this ward. Believe I have a word for it "All this and reclassification too." However, it's not worth it for too long, can you imagine the ups and "downs" that has been my course—Army-wise—and yet—how I still retain the faith that eventually I will be shifted to that branch of the service where all my "officers" feel I definitely belong. 'Tis quite an experience but I do believe I can take it. I sorta feel like a martyr here—Yet let us say—this is the Army—and strange things do occur oft-times as a result.

Would be interesting for the cause of posterity—to show my good business associates and friends a picture of myself midst these iron-bar surroundings. E. has now become Dr. Jekyll—the change from a complacent being to a harried—distraught personality. Ha. Ha. I would like to see their expressions upon being apprised of the above. (In a whisper—for fear I might take my life in my hands—am not even allowed a knife or a fork. However, one can eat with a spoon and like it.) The nurses are sure coöperative and evidence their patience with all of us *i. e.* always at our beck—call. Sh—I'm no problem—yet? . . . .

TUESDAY AFTERNOON
Time unknown

DEAR R.

Your references ("amusing and uplifting") as to the condition I presently find myself in—certainly afforded me to use the vernacular a "Kick"—aside from my mother and B. nobody is aware of that E. of "old" who now is languishing away in a hotel room (I mean a different kind of room only kinda locked in)—because all this strikes me so funny—definitely jocular in note—'Tis no strain to withstand this newly foisted way of living which has been invoked upon me. Believe though—if I was a "Victim" really allergic to some nervous disorder or call it some obsession or fixation then verily would this amount to a harrowing, nerve-wracking experience. As B. in her way describes it—as a stunt—so I gather unto myself better spirits to continue on with this hoax. Never within the stretch of my imagination or of those many friends who knew me—could I ever be pictured as a "depressed being" and no doubt B. informed you as to the ruse or method employed before I became ensconced in this strange den of mine. . . .

It's certainly a case for the Book. I believe I have a name for it—"All this and reclassification too." Be assured that I still retain those Happy Spirits, my Design for living—and above all—I can take it. It is my fervent hope that I may be reclassified and thusly shall I be enabled to do that type of work which I am best fitted for (but *never* do I want a C.D.D.—no matter if I was over age—this would apply) . . . .

Time—Thursday afternoon
Scene—Lounging around in a Ward

DEAR J.

Received your characteristically well-seasoned and spicy letter today—and whilst under the spell of its charming contents contained there-in do I hasten to answer same.

I sure would like to have seen the expression on your face when you noted the return address. Yes E is now hospitalized—and at the same time very healthy. Quite an anomaly—but somehow that seems to be the case. This situation was affected by an interview I had with the Major regarding an obsession—which I led him to believe was a verity—Naturally you must be wondering what I'm up to now. It resolves itself to this question "whether I'm destined to remain in the infantry or be transferred unto that branch of the service—to which I would be fully devoted and at ease. Was too impressive and dramatic in dwelling upon my sad condition—with the result that immediately was I placed in a ward under observation. . . . . Apparently—I who has

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always been the master of words—now find myself indicted by them. With it all I cannot complain and am taking this lazy-much-ado-about-nothing existence in stride. 'Tis quite an experience to find yourself in a hospital when you're rarin-to-go. Imagine this ever happening to me in civilian life. It seems that in the Army—at the slightest provocation—you're suspected—especially when I mentioned—"one half of me doesn't know what the other half is doing." Don't laugh too heartily. I promise you this that at our next reunion—many will be the laughs occasioned by this strange coincidence—(with the help of a "few drinks" to help the story along). So why write about it—Let's give it a heading "All this and Reclassification too." . . . .

The patient affected an elaborate vocabulary both in conversation and in his writing, but frequently misused words and succeeded only in ornamenting his native ingenuineness with somewhat inappropriate trappings. He unblushingly declared that he was "perfectly calm and relaxed," although everything about him screamed of tension, impetuosity and barely restrained emotional and motor outbursts. He manifested a certain child like candor that prevented his disguising his real feelings even in his own interest, and in alternative phraseology admitted to essentially everything he had told "the Major" on his initial visit to the out patient clinic, with the single exception of suicidal ruminations which he completely denied. Regarding his statement that "one half of me doesn't know what the other half is doing" he explained: "You can feel so abject at times that you are sort of vacillating within yourself whether you are doing right here (pointing to one side of his trunk) or doing right here (pointing to the other side). You don't know what course to take. I used it only to emphasize the situation. It sounds ridiculous but you know what I mean. ' You get a kind of feeling that way sometimes."

Direct enquiry was useless with him since he replied in the negative to every query that had in his opinion the slightest overtone of abnormality. There was, however, no reason to believe that he experienced hallucinations. Projectional notions, or a systematized delusional structure were not evidenced, he most assuredly was no hypochondriac and there was at no time any flaw in his general sensorium. His intelligence was somewhat above average. He was unstable, highly keyed, precariously adjusted; a decidedly immature individual who had lost what security he had created for himself in civilian life and was genuinely out of his psychological depth in his present assignment in the Army. He had been attempting unsuccessfully to effect his own "cure," that is to re-create his civilian environment insofar as this was possible by getting into the Quartermaster Corps.

It is doubtful that this man would have come to a psychiatrist's attention in civilian life. The very defects of his personality were in some measure responsible for his material success, his "high-pressure" temperament, his lack of objectivity, his sublime assurance that he was always right. It was by no means incomprehensible that he would have continued piling up profits for his employers, earning his handsome salary and devoting himself to "normal pleasures," to religion, and to superficial love affairs for the balance of an honored and productive life. Those accidents of Fate which bring misfortune and trials to one may just as readily bring ease and comfort to another. Every reed is not leaned upon, every human defect tried in the fire. It is well for us all that this is true. E.F. was no soldier and the very roots of his personality would have been dug up in making him one, still as a perpetual civilian in uniform the Army may yet have good of him.

I have no answers to the questions raised in this paper, nor do I know where to find them. Out of my military inexperience certain possible means of simplifying and making more expeditious the tasks of the Army psychiatrist occur to me, and out of my naiveté, certain suggestions of a visionary nature regarding experience and a body of training that could make the medical officer in this field more valuable to the Army.

1. There seems to be every reason for tightening induction examinations. Every inductee could, if the machinery were suitably set up,

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have a reasonably adequate psychiatric examination before taking the soldier's oath. This subject is, of course, readily expandable into another monograph. From the point of view of the present paper, the local psychiatrist would inevitably be in a better situation to pass on the health of potential soldiers in his own county or even in his own state than on the status of the men in anonymous olive drab whom he meets later in military hospitals. With certain gratifying exceptions this is not being done.

2. More careful classification of recent inductees. I cannot escape the belief that certain men have had to be discharged from the Army on psychiatric grounds who could have been useful soldiers if their capabilities and needs had been accurately understood at the beginning of their service and their placement had been more selective.

3. Greater rapidity in the administrative consummation of discharges once they have been approved by competent hospital boards. It would appear that service records could be completed with greater dispatch and that the number of hands through which the recommendation for discharge now passes before final approval could be reduced.

4. Establishment throughout the country of Recruit Reception Centers patterned after one at present functioning in a mid-Western State and headed by a commanding officer of noteworthy vision and understanding, assisted by a permanent cadre of efficient officers fully acquainted with and sympathetic to his aims. Enlisted men are quartered in small units and receive an unusual degree of personalized attention from their officers. Classification is a deliberate and careful process. Professional psychologists and college graduates who have majored in psychology, of non-commissioned rank, live in intimate contact with the men and rotate in groups of 2 for regular tours of duty on the psychiatric wards of the Station Hospital. Here they receive daily lectures from the medical officer as well as regular assignments in the investigation of patients currently hospitalized. Their records are reviewed, criticized and often made a part of the individual patient's chart. The psychiatrist is in the most intimate contact with the military training center and joins with the officers and psychologists at frequent informal conferences where both individual problems of recent inductees and general policies of the center are discussed.

5. Closer contact between line officers, chaplains and psychiatric staffs. It is at present rare for a patient's commanding officer to visit the hospital for discussion of his problem and I am afraid unheard of for a psychiatrist to go to the patient's company area in search of first hand information regarding him. The chaplain is, not infrequently, the first man whom many of the patients consult regarding their difficulties. Since there is no established military provision for this information to be passed on, it often fails to reach the psychiatrist. Regular conferences of psychiatrists, line officers and chaplains conducted for the purpose of common education might well facilitate the work of all.

The author wishes to express his appreciation to Colonel Harry H. Towler, Commanding Officer 1322 Service Unit, for his courtesy in making possible the clinical studies incorporated in this report.

CONVULSIVE SHOCK THERAPY IN INVOLUTIONAL STATES AFTER COMPLETE FAILURE WITH PREVIOUS ESTROGENIC TREATMENT*

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Thousands of patients with psychiatric disorders occurring in middle age and in involutional and presenile periods of life are constantly being treated with estrogenic substances. Many physicians believe, for example, that involutional melancholia is caused by ovarian deficiency. It is a daily incident to examine female neurotic or psychotic patients of all types from 30 to 60 years of age and hear that some doctor said their disorder was caused by "the change of life."

It has been our experience that estrogenic therapy has no value in these disorders; valuable time and large sums of money are needlessly lost; and eventually most of these patients require adequate psychiatric therapy for lasting recovery. We have therefore reviewed out records in order to compare previous estrogenic therapy with later combined psychiatric and convulsive shock therapy.

For over 25 years, many reports have indicated favorable results from administration of ovarian substances in involutional psychoses. Strecker *et al.*[13] in 1922 reported encouraging results from use of corpus luteum and ovarian substances in involutional melancholia. Pharmacologically, these substances have been proved to be inert. More recently Werner,[15] Hawkinson,[8] Suckle,[14] Mazer,[9] Perusse,[11] Burlingame and Patterson[4] have all reported favorable results. Werner[15] and associates in 1934 reported not only relief of those suffering from actual menopausal symptoms and autonomic disturbances but also recoveries from involutional melancholia. Only cases treated for 3 months or longer were reported.

Burlingame and Patterson[4] in 1941, reporting results of estrogenic treatment in 139 patients, said: "The most favorable results have been obtained in the depressions of the climacterium." Of this group, 60% showed some improvement in about 40 days. This improvement they ascribed to estrogenic therapy, although they state it was only part of the treatment employed; and yet they omit the rest of the treatment program. Davidoff and Goodstone[6] in 1942 recommended the use of estrogens in the mild involutional psychoses which contain features resembling normal menopausal symptoms; 62% of their patients improved.

Recently, Davidoff, Reifenstein and Goodstone[7] reported the treatment of 60 female patients, 45 of whom were given diethylstilbestrol.

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They concluded that their results "indicate clearly that estrogenic therapy is most beneficial in involutional psychoses of the simple type." However, they do not give their criteria for diagnosis of these cases except to call them "depressions occurring in middle life and later years without evidence of organic intellectual defects or without a history of previous depression." Neither do they give the total length of time during which treatment was administered. They do admit more than moderate discomfort from toxic effects in 22 of the 45 cases treated with diethylstilbestrol.

Danziger,[5] who reviewed 164 such cases in the literature and added 7 new ones, gives a more critical evaluation: "Recovery or marked improvement in only 48% of a reasonable large series of adequately treated patients leaves something to be desired." He adds, "Estrogen therapy cannot be specific for involutional melancholia in the female in the present state of ability to diagnose the disease."

It is well known that spontaneous recoveries occur within about 9 months in 40 to 50% of true involutional depressions. Improvements in 60% of cases, as reported by various authors, is therefore, of no significance, especially since any treatment procedure whatever carries psychotherapeutic value. All such favorable reports tend to mislead, and, in our opinion, result from wishful thinking in therapeutic evaluation. Overwhelming factual evidence now shows that not 40 to 60% but a consistent 90% of depressive patients improve in a much shorter time with combined shock therapy and psychotherapy.

In 1938, when one of us (A.E.B.)[1] first reported consistently favorable results from convulsive shock therapy in all types of depressions, he stated: 'In all previously tried chemical, endocrine or shock therapy methods, such as hematoporphyrin, estrogenic, testicular or pituitary hormones, fever therapy and narcosis, no consistent effect in shortening the course of depression has been observed." He later reported[2] that 90% of severe depressions, especially involutional melancholia, clear up within 3 to 4 weeks after 6 to 8 convulsive shocks. Since these reports, many have confirmed these results and the specificity of the treatment. Even the most enthusiastic supporters of endocrine therapy do not claim relief for such a high percentage in so short a time.

Ripley, Shorr and Papanicolaou[12] in 1940, and Palmer[10] in 1941, have stated that endocrine imbalance is not the primary nor rarely a significant factor in the development of mental disorders. The prepsychotic personality factor and the psychobiologic makeup of the individual plus precipitating psychogenic factors are of major causal importance.

Palmer's report[10] in 1941, elaborates these factors pointing out again that the potential involutional melancholiac betrays certain telltale personality characteristics throughout life. These individuals show rigidity in their personality makeup even in its earliest phases. This fundamental rigidity of personality causes resistance to psychic trauma and induces strong protective measures; such individuals lead constricted, narrow lives without mood swings or emotional upheavals. Their faulty personality traits remain the same throughout life; that

is, they may be chronically worrisome, compulsive or perfectionistic, but they do not correct or clear the mental horizon by changing mental trends. The psychotic phase is a culmination at middle age of the lifelong process and is prompted by the numerous psychic traumas of these years. Failing health, loss of productiveness, loss of relatives and friends, diminished vitality, fear of chronic organic disease, fear of sexual failure are only some of these psychic precipitating factors.

In our study, about 500 case records of psychoses and psychoneuroses occurring in female patients between the ages of 31 and 65 during the years 1937 to 1943 were reviewed. Cases which had received estrogenic hormones as therapy for the mental disorder were collected. Seventy-five consecutive cases were obtained. These individuals had all received varying amounts, usually large, of estrogenic hormones over varying periods of time without benefit. On the contrary, they frequently got worse. These patients subsequently arrived in the psychiatric department for hospitalization and rational psychiatric treatment. Of these 75 cases, 41 were classified as involutional melancholia; 12 manic-depressive, depressed type; 20 psychoneuroses with anxiety and depressed features and 2 schizophrenia.

TABLE 1.—INVOLUTIONAL MELANCHOLIA (41 CASES)

	Average	Range
Age	49.9	40 to 65
Duration of illness	1 yr. 10 mos.	1 mo. to 12 yrs.
Length of estrogenic treatment	9 mos.	1 mo. to 4 yrs.
Duration of hospitalization	47.2 days	15 to 202 days*
No. shock Rx	8	3 to 22
Relapses	9 (5 recovered)	
Duration and type of recovery	1 yr. 3 mos.†	3 mos. to 5 yrs. 9 mos.

* The patient in residence 202 days was given a course of theelin in oil in the hospital but made no progress over 5 weeks time. She was next started on insulin shock treatment, without progress. She was then given 22 combined insulin-metrazol treatments with considerable clinical response but she gained no insight and promptly relapsed on leaving the hospital. This case is considered a complete failure.

† Social, 12; full, 25; total, 37 (90%).

Six patients in this group showed definite increase in their difficulties with the administration of theelin. This was particularly true in those who had outspoken sexual conflicts. Five patients who relapsed made either full or social recoveries with further treatment. Four patients were considered complete failures. One patient made a full recovery and was well and active for a year, when a recurrence of depression ended in suicide. It is of interest to note that those patients treated in the years 1937 to 1940 inclusive, spent an average of 66.4 days in the hospital; while those treated in the years 1941 and 1942 inclusive averaged only 39.9 days. This decreased time suggests improved treatment techniques, including the change from metrazol to electroshock. Three patients of this group were treated with psychotherapy alone. The following case is typical of this group.

Case Study. CASE 1. J.T., female, age 47, married. The history obtained from the husband indicated that the patient was a very conscientious, meticulous, rigid personality. She had been operated on 12 years previously for

tumor of the stomach; 9 years previously she had had a cholecystectomy. Recovery from both operations was uneventful. The couple had no children but had adopted their 6 weeks old niece. The husband dated the present illness back 5 years when the patient was about 42. Their mode of living, though somewhat restricted, was entirely satisfactory including marital adjustment, until this time when the patient became mildly depressed and progressively frigid. During the last 3 years before admission she had become increasingly incapacitated because of restlessness, depression, insomnia and anorexia. For 7 months prior to admission her home physician gave weekly treatments of 10,000 units of theelin; her symptomatology increased. She was then brought to the psychiatric unit and treated with tubs, massage, vitamins and insulin for weight gain. There was no relief of the psychologic condition after 5 weeks of treatment.

Immediate affective gain followed 5 curare-metrazol treatments but on referral to an ophthalmologist for eye examination an acute panic state developed. Therefore 5 more shock treatments were given with full social recovery. However, her insight was markedly limited. At the end of a year and a half mild insomnia and complaints of inward nervousness and agitation recurred. She was readmitted to the psychiatric unit and given 5 electroshock treatments combined with curare over a period of 17 days. She was dismissed in excellent condition with considerably more insight. For the past 2½ years she has been entirely well, has done all her own housework and has assisted her husband with farm work. Recently she reported helping to harvest the corn crop, work which she had not been able to do the past 8 years. She has gained 50 pounds in weight.

TABLE 2.—MANIC DEPRESSIVE PSYCHOSIS, DEPRESSED TYPE (12 CASES)

	Average	Range
Age	46	37 to 61
Duration of illness	1 yr. 2 mos.	2 mos. to 3 yrs.
Length of estrogenic treatment	4.2 mos.	1½ mos. to 1 yr.
Duration of hospitalization	42.5 days	10 to 62 days
No. shock Rx	8	5 to 12
Relapses	2	
Duration and type of recovery	1½ yrs.*	4 mos. to 4 yrs.

* Social, 3; full, 9; total, 12 (100%).

The course of the patient remaining in the hospital 62 days was interrupted by 2 weeks of febrile disease. One patient in the group was treated by psychotherapy alone. Three patients showed a definite increase in their psychic difficulties with the administration of estrogens. Both patients who relapsed subsequently recovered with further treatment and have remained well. The following case is typical of this group.

CASE 2. L.B., female, age 47, single. Medical history showed pneumonia at the age of 4 and a pelvic "eviscerotomy" at the age of 45. The patient's personal history showed a stormy developmental period. At the age of 7 she lost her father by death and 5 years later, her mother. She took these losses very severely and was depressed. In school she made a good adjustment, was friendly and sociable but was obliged to give up nurses' training because of an overly-sympathetic reaction to her patients' ills. She completed business college successfully and adjusted well to a secretarial position. Her hobby was fancy and figure ice-skating with many exhibitions. In adult life she had an open, friendly personality but was inclined to be sensitive. Serious depressions followed two unhappy love affairs. A flirtation with her employer brought on a third depression together with loss of self-confidence, severe self-condemnatory ideas and syphiliphobia. She was depressed, seclusive, agitated and actively suicidal with many guilt feelings over physical contacts in her skating

exhibitions and in the flirtation with her employer. Large quantities of estrone, stilbestrol and gonadogen given for a period of 1 year markedly increased the sexual tensions.

After admission to the psychiatric department and before therapy was begun, she made a serious attempt at suicide. Seven curare-electroshock treatments were followed by an excellent affective response. Intensive psychotherapy and bibliotherapy enabled her to develop good insight. She was dismissed on the 46th hospital day as fully recovered. She has maintained her recovery for the past 8 months without further treatment, is working full time and carrying on her former social activities.

TABLE 3.—MIXED PSYCHONEUROSES (20 CASES)

	Average	Range
Age	42.5	30-69
Duration of illness	5 yrs. 9 mos.	6 wks. to 20 yrs.
Length of estrogenic treatment	1 yr. 3 mos.	6 wks. to 10 yrs.
Duration of hospitalization	38 days	15 to 84 days
No. shock ℞	5	5 to 15
Relapses	2	
Duration and type of recovery	1 yr. 9 mos.†	4 mos. to 5¼ yrs.

* This group consisted of 8 reactive depressions, 7 anxiety states, 3 chronic invalid reactions and 2 patients with conversion hysteria.

† Social, 10; full, 8; total, 18 (90%).

The patient whose hospitalization was prolonged to 84 days was treated with conservative therapy for 5 weeks before metrazol shock treatment was instituted. Thirty-three days after shock treatment was begun she was dismissed as a social recovery.

One patient with reactive depression following the loss of all the members of her family attempted suicide prior to admission. Under treatment she regained normal affective tone but relapsed within a 3-month period and committed suicide. The two relapsed patients were complete failures. Seven of these patients were treated by psychotherapy alone. The following case is common to this group.

CASE 3. M.M., female, age 41, married. Her medical history is typical. She "almost died" of malaria at the age of 9. At 18 an exploratory laparotomy for chronic right lower quadrant pain was done and the appendix and right ovary were removed without relief. At the age of 20 she went to a "society doctor" who made a diagnosis of a growth in the vagina and treated her with daily manual massage; she voluntarily stopped treatment upon finding out that he was a quack. At 21, the patient was again operated upon for adhesions because of continued right lower quadrant pain. Part of the left ovary was removed and a curettage was done to relieve chronic backache. Infection of the abdominal wall kept the patient bedfast for several months. At 26, the patient lost her mother. Another curettage was done for backache and the vagina was packed to push the uterus into place. When she was 28 a trip to California was prescribed for nervousness. At 35, her menstrual periods became irregular, on 2 occasions were precipitated by minor accidents. Thereafter she spent a few days in the hospital each year for various complaints.

Six weeks prior to admission to the psychiatric unit, the patient had severe insomnia, gastro-intestinal upsets and spells of nervousness. Within this 6-weeks period she used 500 three grain capsules of sodium amytal and was given 25,000 units of theelin weekly, with additional ovarian extract by mouth. The sexual history shows early sexual traumas inflicted by the patient's father and a hired man, with marked interference in psychosexual development and with subsequent poor marital adjustment and extramarital affairs. She responded rapidly to psychotherapy and was dismissed after 41 days of hospitalization markedly improved. Her excellent adjustment has persisted for over 5 years.

Two cases were diagnosed as schizophrenia of the paranoid type. From a psychiatric view, estrogen treatment was obviously not indicated. However, one patient had had surgically induced premature menopause and received estrogens for 3 years. The severe menopausal symptoms were partially controlled, but the schizophrenic reaction was not affected.

Treatment Given. On admission, patients were given exhaustive general physical and laboratory studies with a period of psychiatric observation in an attempt to establish rapport and seek conflictual material before instituting shock treatment. Of the 75 patients, 64 received some form of shock therapy but in 11 cases psychotherapy alone sufficed. Since the introduction of curare,[3] its use has been routine, first with metrazol and later with electroshock to avoid traumatic complications. A course of from 6 to 8 shock treatments over a period of 2 to 3 weeks is the rule. During hospitalization adequate nutrition is rigorously managed, and in the underweight group subshock doses of insulin are used to stimulate appetite.

We consider the use of sedative therapy valueless; sleeping habits are carefully watched and controlled without sedation. During treatment the patient is isolated from relatives and friends. All activities, including occupational and recreational activity and bibliotherapy are prescribed individually. Following active shock treatment, patients remain in the hospital from 10 days to 2 weeks for reëducative psychotherapy. After dismissal, patients are followed through office interviews as necessary. In the occasional case of relapse the patient is readmitted or treated as an outpatient.

The consistent change in affect of these patients following convulsive shock therapy proves a near specificity of method never heretofore seen in psychiatric therapy of these disorders. However, it has been found that many patients have relapses or recurrence of their disorder at a later date unless psychogenic problems have been solved by psychotherapy. It is a necessary adjunct to shock treatment.

We no longer consider convulsive shock therapy dangerous in the presence of cardiac disease, arteriosclerosis, or changes due to the aging process, when curare is used to soften the convulsive seizures. While hazards are increased by these factors, softening the convulsion certainly minimizes the strain upon skeletal, visceral and vascular systems.

Conclusions. Seventy-five consecutive cases of midlife and involutional mental disorders were obtained from the study of about 500 case records. All of these had received varying amounts of estrogenic hormones without benefit.

This series was treated with convulsive shock therapy and psychotherapy or with psychotherapy alone, combined with thorough psychiatric supervision. Under this treatment, 90% showed social or full recovery in 4 to 6 weeks.

Estrogenic hormones have no place in the treatment of psychiatric disorders except for symptomatic relief of vasomotor symptoms. Convulsive shock therapy is a near specific for the relief of all types of affective disorders, especially involutional melancholia.

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These facts need wider dissemination before the general and psychiatric professions to save time and expense of needless non-scientific treatment in this misunderstood group of patients. Estrogens should further be condemned because they may be harmful and often make the psychiatric disorder more severe.

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THE ENDOCRINE FACTOR IN HOMOSEXUALITY

Report of Treatment of 4 Cases With Androgen Hormone

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It is now realized that homosexuality is very widespread among all classes of society and furthermore that it is apparently on the increase. According to some authors, its increase seems to have paralleled the growth of civilization. Thus Alfred C. Kinsey[3] states "that something between one-fourth and one-third of all the males in any mixed-age group has had some homosexual experience." Among primitive peoples and savages, homosexuality appears to be almost non-existent.

Various theories have been presented to explain homosexuality. The explanations proposed have varied from the purely physical to the purely psychologic. Krafft-Ebing[4] believed in the hereditary basis while Hirschfeld[2] proposed a "psychoglandular" condition as the underlying factor. Freud[1] postulated still another theory: namely, that homosexuality in substance was the result of an imperfect or abnormal solution of the Oedipus complex and castration complex in the case of the boy and of the Elektra complex in the case of the girl. Many of Freud's disciples have suggested considerably different views.

However, they all agree that the psychodynamic approach to the study of homosexuality tends to show the importance of the psychosexual experiences of childhood in determining the future sexual behavior of adolescents and adults. In particular, according to most psychoanalysts, the development of the homosexual can be traced back to the unwholesome personal relationships between parents and their children existing in the home.

It would take us too far afield to present all the objections and criticisms that have been raised against this point of view. Suffice it to say that even Freud finally admitted that in many cases of homosexuality a constitutional (endocrine) factor is present.

Homosexuals have been usually divided into two broad groups, overt and latent. The overt homosexual, as the name implies, is one who has committed homosexual acts. The latent homosexual is one who has not as yet committed any homosexual act but whose behavior can only be explained on the basis of repressed homosexual drives. Such individuals as a rule, sooner or later, resort to overt homosexual practices.

Probably a better classification and one that might avoid some of the criticisms directed at the purely psychoanalytical concept of homosexuality is that of innate and acquired. The psychopathology of acquired homosexuality may be correctly explained on the psychoanalytic basis as outlined by Freud and his disciples. The condition of the innate homosexual, on the other hand, can be best explained on the basis of the presence of a somatic factor in the form of an endocrine disorder.

Anthropomorphic studies as well as endocrine studies have not revealed a specific body structure that is characteristic of the homosexual. On the other hand, the passive male homosexual has certain mannerisms of speech and gait and actions that stamp him as "sui generis." The "fairy" is easily recognized. To a lesser extent, the same is true of the masculinized female homosexual. These structural changes are readily correlated with disturbances in the functioning of the endocrine glands, principally the pituitary gland and the gonads. In this connection, the studies of the androgen-estrogen output of homosexuals have been very illuminating. Thus Neustadt and Myerson,[6] in a quantitative sex hormone study of 29 overt homosexuals, found a marked disturbance in the normal androgen-estrogen ratio. The deviation from the norm took one of two directions: (1) a decrease in the androgens combined with a normal amount or excess of estrogens; or (2) a normal amount of androgens combined with an excess of estrogens.

The experiments of Young and Rundlett[8] may also be cited in this connection. These experimenters produced homosexual activity in spayed female guinea pigs by treatment with estrogen and progesterone.

In the case of the innate homosexual, the endocrine factor is predominant. As a result of the endocrine dysfunction, the individual develops abnormally both structurally and functionally. His physiologic and psychologic functionings become markedly disturbed with

resultant distinctive abnormal behavior. The direct effects of the endocrinopathy, therefore, is to cause the individual to stand out as a sexual deviate. However, in addition to these direct effects, there may be indirect effects which may still further modify the individual's behavior and personality.[5] These indirect effects are dependent upon the individual's emotional reactions to his own deficiencies. How the individual will react in such a case will naturally depend upon his previous emotional and social experiences. Hence, no two individuals will necessarily react in the same manner to the same defect.

The fact that there is usually a diminution in the secretion of the androgen hormone in male homosexuals has strengthened the belief of the importance of the rôle of the endocrine factor in the causation of homosexuality, and has given impetus to the possible therapeutic value of the male sex hormones in the treatment of such cases. The homosexual is an unadjusted individual. Every homosexual act is a delinquent act and is so labeled by society. The homosexual very often also becomes involved in criminal acts of the most sordid type. Any treatment that offers relief in these apparently hopeless cases is worthy of a trial. There have been many reports in the literature concerning treatment of homosexuals with various endocrine preparations. Some of the earlier reports of the results of this type of therapy were unfavorable. The recent reports, however, are much more encouraging. The better results may be due to the fact that more active and potent preparations of androgen hormones are now available.

Thus, for example, C. A. Wright[7] reports the results of endocrine treatment in 14 male homosexuals. The hormone assays in all cases showed a very marked diminution. After treatment, with androgen hormones, however, they all showed an increased androgen output. Coincident with this change, an improvement was noted in the sexual behavior of 9 of the patients, 3 of them claiming to have become normal. Four reported improvement from other causes than the endocrine treatment. One reported no improvement.

The following 4 cases are reported to show the effects of androgen hormone therapy in adolescent male homosexuals.

Case Studies. Case 1. W.H., a white boy aged 15 years, 9 months, was referred to the Child Guidance Home for observation because he was a serious delinquent. His delinquencies had started a year previous to his admission. At that time, he burglarized a home. From then on his delinquencies increased in frequency and in magnitude. He was brought to court for the first time because he had run away from home and had been involved in a hold-up. In addition, he had presented a problem at school for a considerable period of time. He truanted frequently and his academic achievement was not on a par with his intellectual capacity.

The boy's developmental history was essentially normal. He had had the ordinary diseases of childhood, but apparently with no serious complications.

The parents described William as being personally very clean, meticulous, and particular. He was interested in athletics and enjoyed swimming, fishing and camping. He never had many friends and never any close friends. He seemed to prefer the seclusion of his own company. He had never shown more than a casual interest in girls. Although he knew how to dance, he made no effort to go to dances or to parties. When he was about 14 years of age, he made the acquaintance of a boy his age to whom he became closely attached.

At home he was very domineering and insulting. He came and went as he pleased and when questioned, threatened to run away. He had always been subject to temper tantrums.

Even in grade school he was considered sneaky, insincere, untruthful, underhanded and impudent. He showed no interest in his work, but always managed to pass. In high school, he was also difficult to control and showed an immature type of behavior. When thwarted, he would resort to temper tantrums in the classroom. On several occasions he carried a loaded gun to school.

It was during his high school days that he began to rob and steal. The delinquencies in which he was involved have apparently always been in the company of his one close friend whose acquaintance he made at high school. On one night, the two boys burglarized 5 homes. Very often they remained away from home all night sleeping in the woods.

When apprehended by the police, the boy was very sarcastic, insolent and arrogant. He threatened to shoot certain people at the first opportunity. This applied especially to the police and his parents.

The social background in this case was apparently of the best. The father was a highly intelligent man who had always been a good provider. He was earning about $10,000 a year. He was greatly concerned over his son's antisocial behavior, but was unable to offer any explanation for it. He had always been under the impression that their relationships had been very good and could not understand why the boy had turned against him. He was completely bewildered at the turn that events had taken. He reiterated over and over again that the boy had everything he needed at home and therefore there was no reason for his stealing.

The mother was a personable individual who made a very good impression. She appeared kind and firm. It was apparent that she was the disciplinarian in the home. She appeared to be emotionally untouched by her son's difficulties. The home atmosphere was congenial, the only quarreling occurring between the patient and his younger sister. The latter was a very intelligent girl who presented no problem either at home or at school.

The physical examination of the boy, including the neurologic examination, was essentially negative. The urinalysis, complete and differential blood count, blood Wassermann, and tuberculin tests were all normal.

The endocrine examination revealed a hypogonadal status. The boy showed the eunuchoid type of skeletal development. He was 69 inches tall (2 inches above the average for his age) and his span was even greater, being 72½ inches. Interestingly, his bone age was only 14 years, showing that he had great possibilities for continued linear growth.

His voice was still high-pitched and there was no sign of a beard on his face. His gait and mannerisms were effeminate. The genitalia were exceptionally large with a female hair line. Basal metabolic readings were minus 2% and minus 5%. The glucose tolerance results were as follows: 106 mg., 131 mg., 93 mg. and 90 mg.

On the Standard Revision of the Simon-Binet test, the boy received an intelligence quotient of 120, thus rating him as an individual of superior intelligence. In his answers, however, there was a wide scatter of successes and failures, which was highly significant in view of his social immaturity which was startingly shown when he was tested on the Vineland Social Maturity Scale. On this scale, he rated as sub-average, his social quotient being 82.9.

The behavior of the boy while at the Child Guidance Home was that of an immature, effeminate and indecisive person. He was shy and timid and at first tended to withdraw from the group. He never engaged in any boys' games. Later he became very friendly with the much smaller and younger boys to whom he began to boast about his escapades. He bragged about the number of robberies he had committed and stated that there was no need to be afraid of committing such acts if one carried a gun. He also boasted about his pipe-smoking but privately admitted that it made him sick. He annoyed the younger boys by his attempts to kiss them and to fondle them. On several

occasions he and another boy were found in compromising positions in the dormitory. Another effeminate boy who was being studied at the Home stated that William masturbated frequently, trying to get the other boys to perform various perversions with him, especially fellatio. He even offered to pay for this service. When one of the older and more masculine boys became ill, William insisted on nursing him. He sat on his bed and ministered to the sick boy's needs in a very motherly and loving manner. In general, in his social relationships he could be described as a highly demonstrative, dependent woman.

In the course of interviews, William admitted that he stole because he wanted lots of money and "to bolster my courage." The year before his arrest he had formed a friendship with a very masculine boy of his age who was "very brave and had a great deal of courage." With this boy, William was involved in 30 stealing episodes. William never stole alone. In connection with these episodes, Bill obtained a gun. He admitted that "guns frighten me" but he felt that by "carrying a gun he proved himself to be a man." He and his partner in thefts used to go out on frequent bicycle rides. He admitted that both would masturbate as often as every half hour during these trips. His partner was particularly active. He also stated that his friend had had intercourse but "I get no pleasure out of fooling around with girls." This was said with a great deal of disgust. It was evident that the other boy was the leader and both reckless and fearless while W. was really afraid. W. was extremely jealous of his chum and objected strenuously to the latter associating with other boys.

Another reason advanced by W. for carrying a gun was the fact that he had been frequently accosted by men, especially colored men, who demanded that he perform fellatio on them. It was later brought out that the probable basis for this statement was that his dream life as well as his phantasy life were full of just such adventures, especially of being attacked by negroes.

It was also brought out that he was scared every time he committed a theft, or burglary, but that it was "fun to be scared this way." It gave him the same thrill that he had following an ejaculation.

From additional material elicited during many interviews it was evident that the boy was suffering from the fear of castration by his father. This was an ever-present threat to his security, causing a great deal of anxiety and the constant need to prove to himself that he was still a male. From the psychodynamic standpoint, therefore, some of his behavior could be considered as a compensatory mechanism by means of which the boy attempted to prove his masculinity.

Basically, however, it was apparent that the boy, because of the gonadal imbalance, was an innate and latent homosexual.

Treatment with androgen hormone was commenced. The boy received deep intra-muscular injections of 25 mg. testosterone propionate* 3 times a week for a period of 6 months, after which they were given twice a week for 3 months, and then discontinued entirely.

The results were startling. A decided change was noted in the boy's personal appearance. There was a growth of hair on the face and in the axillæ. The hair on the mons assumed the male configuration. His voice became deep. Interestingly, whereas before treatment he had shown a rapid linear growth, there was a marked lessening in this respect following treatment.

Coincident with these structural changes, there was a marked change in his personality. Instead of a fearful, highly emotional and demonstrative effeminate boy, he became a pleasing type of the aggressive male. There were no more delinquencies. His sexual life also became normal. He fell in love with a girl to whom he later became engaged.

At last reports (4 years after treatment) he was in the armed service of his country where he has made a perfect adjustment.

At no time during the course of treatment was any attempt made to treat

* Neo-Hombreol, supplied through the courtesy of Roche-Organon, Inc., Nutley, N.J.

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the boy psychoanalytically. Psychotherapy was limited to the explanation of the rationale of the use of endocrine medication in his case.

CASE 2. C.R., a white boy of 13, was referred for study to the Child Guidance Home because he had been involved in a series of petty thefts at school. The first stealing episode had occurred 2 years previously, at which time the boy had stolen milk from porches of persons living in the neighborhood. He had also taken 41 books from the school library which he never returned. Various other minor thefts were also reported. In addition, it was noted that he did not associate with other children at school. He kept aloof and showed definite tendencies to withdrawal.

The family history, while not unusual, was interesting. The home was a broken one, the father having deserted when the patient was 3 years old. All the children, of whom there were 5, were placed in a Children's Home. C. who was the youngest remained there for 3 years, which was a considerably longer period than that which his brothers and sisters had stayed. On his return home, he became extremely devoted to his mother, helping her with all her household tasks. The other children immediately nicknamed him "sissy." There was a great deal of financial distress in the home, the economic status being most often just marginal.

According to the personal history, the boy was a premature baby, weighing 3 pounds at birth. His developmental history was entirely normal and no unusual medical incidents had occurred.

In general, the physical examination was essentially negative. The blood Wassermann was negative. The endocrine picture was very suggestive. The boy was of average height but 15 pounds overweight. The fat distribution was principally of the mons-mammary-girdle type. There was no hair on the face or in the axillæ. The genitalia were small, with sparse hair present on the mons veneris. Two basal metabolic readings gave the following results: minus 19.5% and minus 18.2%. His sugar tolerance was definitely increased, the readings on the glucose tolerance test being fasting blood sugar 88 mg., first specimen 121 mg., second 94 mg., and third specimen 87 mg.

On the Stanford-Binet test, C. received an intelligence quotient of 99, ranking him as a boy of average intelligence.

At the Child Guidance Home, it was noted that C. was very effeminate. He talked in a high-pitched girlish voice and walked with a mincing gait. His face was round and his cheeks were rosy. He was extremely neat about his person and always looked clean and well dressed. He did not engage in any rough play with the other boys. He was very easy-going and very seldom asserted himself. He was tractable and easily managed. He had a huge appetite and drank a great deal of water between meals. He always asked for milk. He appeared extremely phlegmatic and very sleepy. He yawned constantly. These characteristics were so marked that he was often asked if he felt ill or tired. He preferred being by himself. When he was alone, he usually sat down and read fairy tales. He was ashamed of this sort of reading but persisted in it nevertheless. He appeared to daydream a great deal. An interesting fact about his fantasy life was that his mother always appeared in them. An outstanding characteristic of his fantasies about his mother was that she usually lived to be 300 years old. The boy admitted that he worried a great deal about his mother. She was hard of hearing and he was very much afraid that she might some day go out on the street and, because of her deafness, meet with a fatal accident. He did not know what he would do without her. He was greatly attached to his mother and was very jealous of his sister when his mother made a fuss over her. It was also brought out that the boy still slept with his mother and until recently would often sit on her lap. The mother, on occasion, sat on his lap. The mother admitted that the boy slept with her, but in extenuation said that she always looked upon him as a girl. When C. was questioned about sex, it was discovered that he was well informed, but that sex as such held very little interest for him. He admitted that he had masturbated occasionally.

In reviewing the findings, it was felt that the boy's asocial and antisocial

behavior was due to both exogenous and endogenous factors. From the psychodynamic standpoint it was apparent that the desertion of the father with the resultant placement of the boy in an orphanage plus the continuous economic stress in the home had given the boy a marked feeling of insecurity. The feeling of insecurity was further heightened by the fact that his only anchorage, namely his mother, was sick and physically handicapped and therefore might be suddenly taken away from him. The economic and social and emotional deprivations could thus readily account both for his antisocial behavior and for the obvious mother fixation.

However, the boy's endocrine condition could not be overlooked. The boy's personality make-up was definitely in line with his glandular make-up. He was sleepy and tired all the time. It was difficult to arouse him in the morning. The boy was sluggish both mentally and physically. That is why he hated school despite the fact that he was of average intelligence. In addition, he was shy, timid, effeminate and lacking in aggressiveness. All these traits are characteristics of the adolescent male suffering from dystrophy adiposo-genitalis. Additional physical characteristics of this glandular disturbance are the increased appetite and abnormal thirst. In this case the boy loved to drink milk and his petty thievery was essentially limited to stealing milk. In other words, his stealing was not that usually associated with hostile aggressive type of behavior. Rather it was a reaction called forth by an inner elemental urge due to a pathologic condition.

The psychopathology in this case, therefore, apparently involved situational factors as well as endocrine factors. It was felt that the boy would profit from psychotherapy and endocrine therapy. Both were recommended, but unfortunately neither was carried out.

Three years later, the boy was returned to the Child Guidance Home with almost the identical complaints. His truancy from school was chiefly stressed. At this time, C. presented a somewhat different picture than the one he had when he was first studied. He had gained markedly in weight and his responses were very slow. His effeminate appearance was even more pronounced than before. He giggled, smiled, rested his hands on his hips, rolled his eyes and tossed his head and expressed indignation exactly the way a girl does. He wore a bracelet which he himself had made. While sitting in the chair, he swung his hips about and held his head in his hands, saying, "Oh! dear, Oh! dear," every time he was asked a question.

Reëxamination of the boy showed that in the past 3 years the boy had gained 42 pounds in weight and had grown 7 inches in height. He was 27 pounds overweight for his height which was average. His face was round and plump. There was no hair on his face. His general appearance was that of a girl. His breasts were large and his hips broad and rounded. The excessive fat was distributed principally over the hips and thighs. The genitalia were normally developed, but the hair over the mons had the female configuration. His B.M.R. was -3% and the glucose tolerance test gave the following readings: fasting blood sugar, 117 mg.; first specimen (often 100 gm. glucose), 121 mg.; second specimen, 121 mg.; third specimen, 95 mg. According to the androgen assay, he secreted 8 I.U. in 24 hours.

In interviews with workers, the boy spoke of his truancy and said that he hated gym because he was ashamed of his body. That was why he played hooky from school. He realized that he was built like a girl. He admitted that he was afraid to play with boys of his age and, although he resented being called a "sissy," he realized that it was a proper nickname. He wished he could be born over so that he could start all over and be a real boy. He denied having had any sex experiences or having practiced any sex perversions. He still slept in the same bed with his mother. Although he went with girls who permitted all kinds of liberties, he never took advantage of his opportunities. He said that he had never had the desire for sexual intercourse. He loved nature, art and good music. He had a passive, submissive, effeminate type of personality.

It was apparent that the boy had insight into his condition and as a result

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had developed a marked feeling of inferiority. This had caused him to seek escape by withdrawing from normal social contacts. The latent homosexual trends were also becoming more and more noticeable.

In view of the outstanding importance of the glandular condition, treatment with testosterone propionate was commenced. The boy, however, was uncooperative, and did not report regularly for his treatments. He became involved in overt homosexual practices for which he was finally apprehended by the police. The boy was terribly mortified and attempted suicide. He wrote a note to his mother in which he said that he knew he was different from other boys and therefore hated and despised himself. All he thought of was suicide.

The boy was urged again to try medical (endocrine) therapy. He consented and this time he coöperated fully. The results were highly gratifying.

His body build soon changed. He lost in weight and his appearance became more rugged and manly. Hair grew on his face and in the axillæ, and the pitch of his voice was definitely lowered. Coincident with these physical changes, there was a change in his personality traits. From a shy, timid, self-effacing, effeminate looking individual he became an aggressive male adolescent. At present he is in the armed forces where he has made a good adjustment.

Case 3. L.B., a white male age 22, was referred because he was extremely nervous. His nervousness took the form of marked instability, hysterical spells and temper tantrums. He was easily angered and often "felt like screaming." When thwarted, he pouted or had temper tantrums during which he would "break things." According to the patient he had been nervous all his life.

The patient was a very slender young man. He was 67 inches tall and weighed 109 pounds. His gait and mannerisms were definitely those of a girl. His voice was very high-pitched.

The general physical examination was essentially negative. The pertinent endocrine findings showed that he had a eunuchoid type of skeletal development. His skin was smooth and fair. The hair was soft and wavy. There was no hair on the face or in the axillæ or on the chest. The genitalia were normal in size but there was practically no hair on the mons veneris. The cremasteric reflexes were absent. The prostate gland was easily palpated. His B.M.R. was −4%, and his androgen output was 10 I.U. in 24 hours.

In conversations with the patient, it was learned that he was attending a school in order to become a "beautician." He "just loved" to beautify women and he thought that it was "marvelous" to be able to make a coiffure. He thought his nervousness was due to the fact that he had a high-pitched voice. He was very conscious of this and justly so. His voice was definitely that of a girl. He had had to listen to the taunts of his friends about his being a girl but, although he raged inwardly, he felt that there was nothing he could do about it. The jibes and jeers were all the more pointed because of his feminine mannerisms and gait. His choice of occupation only served to enhance his female characteristics.

The patient had always been aware of his deficiencies and, as a result, had developed a marked feeling of inferiority and insecurity. At home, the situation was aggravated by the fact that his father had openly rejected him. The father admitted that he was disappointed in his son who from childhood had never shown any inclination to be a "real boy." He had never played baseball or football, neither had he taken part in any sport that was considered rough. His lack of virile masculinity had always been outstanding. The patient admitted that he occasionally had an erection but these occurred very infrequently. He masturbated now and then but he was not certain if there was any emission. There was absolutely no sexual urge. He liked pretty women, but only in the same manner that one liked a beautiful picture. He told with some signs of pride that he had been keeping steady company with a girl but, on questioning, admitted that there had been no sex play between them. In fact, in the 4 years that he had been calling on the young lady, he had not even kissed her once. He claimed that he liked her because she had pretty hair and her hands were very beautiful. Men had made advances to him but he was

both afraid and repelled by their roughness. However, he did confess rather reluctantly that certain men did appeal to him, but he could not exactly describe the emotional state aroused in him by them.

The patient was given deep intramuscular injections of 25 mg. of testosterone propionate every other day for several months. Gradually various changes were noted. Hair began to grow on the man's face and chest as well as in the axillæ and over the mons veneris. His voice began to break. All the symptoms of beginning puberty appeared. The patient reported more frequent and longer erections and later an occasional nightly emission.

Coincident with these developments, there were marked changes in his attitude and behavior toward the opposite sex. He reported that for the first time he was beginning to notice and to comment on the various physical charms of the girls with whom he came in contact. Stranger still, he felt an urge to touch them and to embrace them. His "fiancée" was rather amazed and provoked at his description of the sex allure of the various girls at the beauty parlor where he worked. He atoned for this by becoming more amorous and attentive toward her. For the first time he understood and appreciated the innuendoes in the risqué stories that his fellow workers told. Little by little, as his treatment progressed, he became more and more masculine both in his appearance and in his behavior. One day he announced that he was disgusted with his work; that hair setting was a job for girls and that he would obtain work that was manly. This he proceeded to do. Shortly thereafter he was married. His sex life has been perfectly normal. At the beginning of treatment examination of the semen failed to reveal the presence of active spermatozoa. However, as treatment continued, this condition was rectified and his wife soon became pregnant.

Case 4. R.O., a white boy of 13 was referred by his family physician because of his effeminacy. In school, the other boys called him "sissy" because of his feminine mannerisms, actions, and high-pitched voice.

The personal social and family histories were essentially negative. The same was true of the general physical examination. The endocrine examination revealed the following pertinent facts:

The boy had the female type of skeletal development; the pelvis was broad and he was knockkneed. His waist was extremely small, and his fingers were long and delicate. His skin was fair and smooth. His face was very feminine looking, the skin being very fair and highly colored. There was no hirsutism either on the face or in the axillæ. His breasts were exceptionally large. The penis and testes were normal in size but there was a female hair line.

Androgen determination showed a secretion of 7 I.U. in 24 hours.

From interviews with the boy it was learned that he realized that he was not as masculine as most boys and that he had tried to compensate for this by forcing himself to become interested in athletic sports. In this he had not been very successful. He was more successful in amateur dramatics. He liked to study and was on the honor roll in his class. When younger he played only with girls. He helped his mother with the household tasks and particularly enjoyed helping with the cooking and baking.

At the age of 10 he began to have nightly emissions. These were accompanied by vivid dreams. In these dreams a naked man who was being whipped unmercifully by another man would appear. The boy used to look forward to these dreams, as they gave him a great deal of emotional satisfaction. He did not understand the nature of the emotion that was thus aroused. The men in the dreams were always big muscular broad-shouldered individuals with slender waists.

For the past year he had begun to masturbate during these dreams. Recently the dreams varied somewhat from the original dreams in that the one naked man tortured the other by either burning his penis or by sticking pins into it.

He admitted that several times he had seen boys and men of this particular build naked and that they had aroused a strong sexual urge in him. Girls never aroused him in that manner. He had often seen his mother in the nude but she had never aroused any sexual desire in him.

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Although he had been greatly aroused on various occasions by the sight of nude boys and men, he had always been able to restrain himself from embracing them. Such sights, however, would produce strong erections and a great desire to masturbate.

The boy had practically no knowledge of the anatomy of the female sexual organs nor of the physiology of sex in general. He did not know how the sexual act was performed.

Treatment with testosterone propionate was instituted. Injections of 25 mg. were given 3 times a week. As improvement was noted, the injections were gradually reduced to twice a week. Recently they were discontinued altogether.

The first improvement noted was a change in the pitch of the boy's voice, which became much lower. Hair began to grow on his face and gradually his whole physical contour changed. He lost his feminine curves and his breasts became smaller. The boys stopped calling him "sissy" and began to cultivate his friendship.

Interestingly, he told that, coincident with these structural and personality changes, the content of his nightly dreams had changed. He began having dreams with heterosexual content. A woman entered into the dreams: at first she merely undressed the man and admired his slim waist and muscular build. In succeeding dreams, the woman also undressed. The man would touch her breasts and then they would both go to sleep. These dreams did not excite him and never led to orgasms.

After 6 months of treatment, he began to feel a thrill when standing next to a girl. He noticed that he desired the company of girls more and more. Boys did not thrill him any more in the manner they had formerly. When finally discharged, he was in all respects, a normal male.

Discussion. The need for the psychosomatic approach to the study of homosexuality is demonstrated in the 4 cases that have been presented. Or rather, the term somatopsychic should be used as heretofore, the psychic component has been overemphasized in discussions of the etiology and pathology of homosexuality. The somatic or constitutional factor has not been sufficiently stressed.

If we employ the suggestion of dividing homosexuals into two groups, innate and acquired, it will be seen that these 4 cases can be classified as innate homosexuals. Only one of them had resorted to overt homosexual practices before treatment was commenced. The homosexual trends and drives of the other 3 were obvious and unmistakable. Obvious also was the fact that their innate homosexual drives were due to endocrine dysfunctions. As a result of disturbed gonadal secretion, the boys failed to develop normally both structurally and functionally. Their resultant behavior was such that it stamped them as sexual deviates of the homosexual type. This represented the immediate and direct effects of the endocrinopathy upon the patient's behavior and personality.

In addition to these direct effects, however, there were indirect effects which varied in each case. These indirect effects on the patient's behavior and personality were due to their emotional reactions to the awareness of their own physical shortcomings.

These emotional reactions are very important, as they often furnish the motivation for the individual's behavior toward his social milieu. Very often such motivations are operative at the unconscious level.

How an individual will react to the awareness of an organ deficiency will depend largely upon his intellectual and emotional endowment

and upon the nature of his past experiences. Hence, no two individuals need necessarily react in the same manner to similar defects. This is well illustrated in Cases 1 and 2. Both of these boys were aware of the fact that they were different from other boys in certain specific respects. Each, however, reacted differently to this knowledge. W.H. (Case 1) reacted to his lack of masculinity by developing a marked feeling of inferiority and insecurity for which he tried to compensate by assuming an attitude of superiority. By adopting the rôle of a bandit and gunman, he hoped to prove his masculinity both to himself and to the world.

C.R. (Case 2) also realized his lack of masculinity and also developed marked feelings of inferiority and insecurity. However, his reaction to this situation was different from that of W.H. (Case 1). Instead of compensating for his feeling of humiliation by developing a hostile, aggressive type of behavior, he became neurotic. His neuroticism manifested itself in various ways, culminating finally in an attempt to escape from reality, first by merely withdrawing from all social contacts and, when this failed, by attempting suicide.

Similarly the choice of occupation by L.B. (Case 3), namely that of hair stylist, can be looked upon as an indirect effect of his gonadal insufficiency.

The differences in the reactions of these boys to the knowledge of their constitutional deficiencies can only be explained on the basis of the differences in their past social and emotional experiences. The importance of these indirect effects can not be overemphasized, as very often they furnish the leitmotif for the individuals reactions to his social milieu.

In all 3 cases, treatment with testosterone propionate brought about both structural and functional changes with resultant disappearance of both the direct and indirect effects, and the development of normal masculine attitudes and trends.

Similar results were obtained in Case 4. In this case, as a result of treatment with androgen hormone, the latent homosexual trends were gradually converted into normal heterosexual equivalents.

Conclusions. Four cases of male homosexuality are discussed and the need of the somatopsychic approach to their understanding is stressed.

The division of homosexuality into innate and acquired is suggested. The importance of the endocrine factor in the former is discussed and the beneficial results of treatment with testosterone propionate in 4 such cases are reported.

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SULFAMERAZINE (2-SULFANILAMIDO-4-METHYLPYRIMIDINE)*

II. SULFONAMIDE CONCENTRATIONS IN THE BLOOD OF MAN PRODUCED BY SMALL, DAILY, ORAL DOSES OF SULFAMERAZINE, SULFAMETHAZINE, SULFADIAZINE, AND SULFATHIAZOLE

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Pharmacological and clinical studies of sulfamerazine[3,5–12,15,17,21] have shown that, following oral administration, a higher concentration in the blood is attained more rapidly and maintained longer than the concentration produced by various commonly used sulfonamides in equal doses. These characteristics of sulfamerazine result from its rapid absorption from the alimentary tract and its slow excretion by the kidney.[21]

The experiments reported herein were designed to permit a comparison of the concentrations of sulfonamide produced in the blood of normal human subjects by the daily administration of a single small dose of sulfamerazine (*2-sulfanilamido-4-methylpyrimidine*), of sulfadiazine (*2-sulfanilamidopyrimidine*), of sulfamethazine (*2-sulfanilamido-4,6-dimethylpyrimidine*), or of sulfathiazole (*2-sulfanilamidothiazole*).

Methods. Eight apparently normal, male laboratory workers, whose weights varied from 55 to 77 kg., were given initially a 2 gm. oral dose of sulfonamide. This was followed by daily doses of 1 gm. each during the succeeding 5 or 6 days. In one series the initial dose was 1 gm. and the sustaining dose 0.5 gm. per day. In each case the initial dose and the daily maintenance dose were given at 8:30 A.M. Using the method of Bratton and Marshall,[1] the concentration of "free" sulfonamide in 0.1 to 0.3 cc. of whole blood was determined at frequent intervals, and the concentrations of "free" and of "total" sulfonamide were determined on one or two 24-hour samples of urine from each individual. Total leukocyte counts were made at the end of the period of higher dosage with sulfamerazine, and at the beginning and end of the dosage periods with sulfadiazine, sulfamethazine and sulfathiazole, in which order the drugs were studied. At least 1 week elapsed between the final dose of one series and the initial dose of the next series.

Results.—In Table 1 are presented the average sulfonamide concentrations in the blood, together with their standard deviations.

* Sulfamerazine was originally termed sulfamerizine.

Although blood levels of 0.5 mg. or less per 100 cc. could not be measured with accuracy, these are included in the averages since their occurrence was rare, except 24 hours following sulfamethazine or sulfathiazole administration.

TABLE 1.—AVERAGE CONCENTRATIONS* OF FREE SULFONAMIDE IN THE BLOOD OF 8 NORMAL MEN FOLLOWING SINGLE DAILY DOSES OF SULFAMERAZINE, SULFADIAZINE, SULFAMETHAZINE, OR SULFATHIAZOLE

			Sulfamerazine		Sulfadiazine	Sulfamethazine	Sulfathiazole
Day	Hours†	Hours‡	Initial dose, 2 gm. Daily maintenance dose, 1 gm.	Initial dose, 1 gm. Daily maintenance dose, ½ gm.	Initial dose, 2 gm. Daily maintenance dose, 1 gm.	Initial dose, 2 gm. Daily maintenance dose, 1 gm.	Initial dose, 2 gm. Daily maintenance dose, 1 gm.
1	..	1	5.6±2.7	3.7±1.2	1.3±0.6	5.9±1.6	2.7±1.8
		2	6.7±2.4	4.6±0.9	2.2±0.8	6.6±1.8	3.8±1.5
		4	7.1±1.6	4.6±0.8	2.7±0.7	5.6±2.0	4.1±0.6
		8	6.3±1.3	4.1±0.7	2.5±0.7	3.8±1.9	2.0±0.5
2	0	24	3.6±1.2	2.1±0.7	1.1±0.2	1.3±0.9	0.4±0.1
3	0	48	3.4±1.4	1.9±0.8	1.2±0.3	0.7±0.6	0.2±0.1
5	0	96	3.3±1.4	2.0±0.8	1.1±0.4	0.6±0.5	0.2±0.1
	2	98	6.3±1.5	4.0±1.2	2.6±0.7	3.8±1.3	1.9±0.6
	4	100	6.7±1.6	4.3±1.0	3.5±0.5	3.0±1.5	2.1±0.4
6	0	120	3.1±1.0	1.9±0.7	1.3±0.3	0.6±0.4	0.3±0.2
	2	122	5.9±1.3	4.2±0.9	3.3±0.9	4.3±1.2	2.1±0.8
	4	124	6.2±1.3	4.2±0.5	3.8±0.7	3.4±1.4	2.1±0.2
7	0	144	3.3±1.4	2.3±0.9	1.3±0.4	0.5±0.4	0.3±0.2
	2	146	6.0±2.0	4.0±1.2	3.0±1.0		
	4	148	6.7±1.7	4 1±1.1	3.4±0.6		
	8	152	6.1±1.7	3.5±1.1	3.1±0.7		
8	24	168	3.6±1.5	2.0±0.5	1.5±0.3		
9	48	192	1.5±0.9	1.0±0.3	0.6±0.1		
10	72	216	0.8±0.4				

* Average concentrations, together with their standard deviations, are expressed in milligrams per 100 cc. of whole blood.
† These hours refer to the time at which the blood samples were taken, in relation to each daily maintenance dose.
‡ These hours refer to the total elapsed time following the initial dose.

The data obtained following the administration of sulfamethazine, sulfathiazole, and sulfadiazine are presented graphically in Figure 1, together with the curve for the same dose of sulfamerazine. The concentration in the blood 2 hours following the initial dose of sulfamethazine equaled that produced by sulfamerazine. However, the concentration of sulfamethazine decreased rapidly, whereas the concentration of sulfamerazine rose slightly during the next 2 hours and then decreased gradually to a level, 24 hours after dosage, of more than twice that of sulfamethazine. The concentration of sulfathiazole, although higher than that of sulfadiazine during the first 6 hours, was lower thereafter, and markedly lower than that of both sulfamethazine and sulfamerazine during the entire 24-hour period.

Attention is directed particularly to the curves in Figure 1, relating to the *last* day of dosage, which day was typical of all days on maintenance dosage (Table 1). The concentration of sulfadiazine was consistently higher than that produced by sulfathiazole in equal dosage, and, except for the 4-hour period following each maintenance dose, was greater than that of sulfamethazine. However, on the same dosage, sulfamerazine maintained a concentration in the blood approximately twice that of sulfadiazine, and several times that of sulfathiazole.

In Figure 2 curves are presented which facilitate comparison of the concentrations of sulfonamide in the blood produced by the dosages of

sulfamerazine and sulfadiazine employed. The greater efficiency of sulfamerazine, in comparison with sulfadiazine, in producing and maintaining sulfonamide concentrations in the blood is shown. Thus, with an initial 2 gm. dose of sulfamerazine, followed by daily maintenance doses of 1 gm., the average daily concentration of free sulfamerazine in the blood of these subjects decreased from a peak of about 6.5 mg. to a low of 3.5 mg. per 100 cc. Following an initial dose of 1 gm. and daily maintenance doses of 0.5 gm., the average maximal blood level with sulfamerazine was about 4 mg. and the minimal about 2 mg. per 100 cc. When an initial 2 gm. dose of sulfadiazine was given, followed by 1 gm. daily, the concentration in the blood rose each day to about 3.5 mg. and fell to about 1.5 mg. per 100 cc.

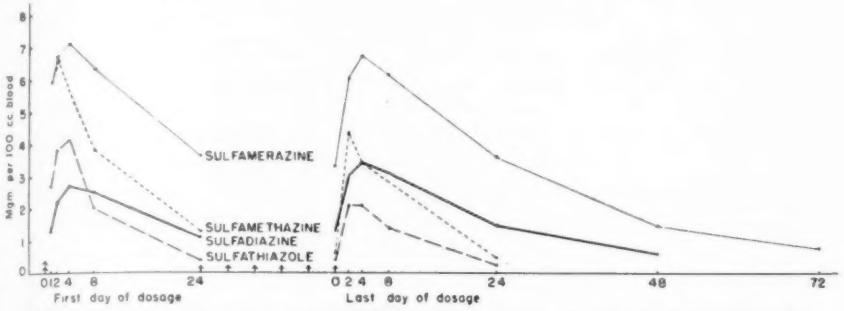

FIG. 1.—The average free sulfonamide concentration in the blood of 8 normal men following the oral administration of sulfamerazine, sulfamethazine, sulfadiazine and of sulfathiazole; an initial dose of 2 gm. of each drug was given followed by a maintenance dose of 1 gm. daily for a total period of 6 or 7 days.

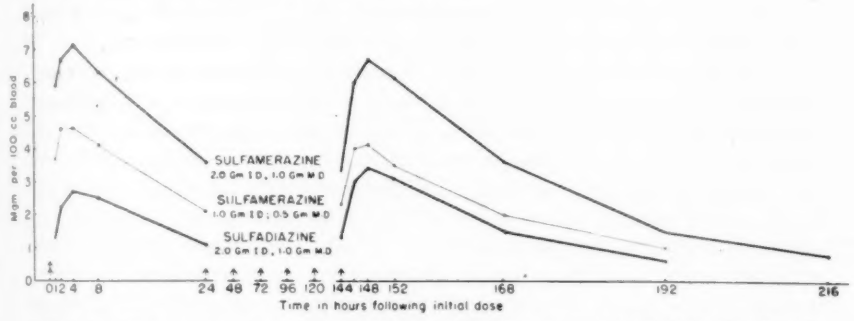
Mgm per 100 cc blood
SULFAMERAZINE
2.0 Gm I.D., 1.0 Gm M.D.
SULFAMERAZINE
1.0 Gm I.D.; 0.5 Gm M.D.
SULFADIAZINE
2.0 Gm I.D., 1.0 Gm M.D.
0 1 2 4 8 24 48 72 96 120 144 148 152 168 192 216
Time in hours following initial dose

FIG. 2.—The average free sulfonamide concentration in the blood of 8 normal men following the oral administration of sulfamerazine and of sulfadiazine once daily for a period of 7 days. The blood levels shown are those resulting from the first and last days of dosage. (I.D. = initial dose; M.D. = maintenance dose.)

These data indicate that the dosage of sulfamerazine necessary to maintain any reasonable concentration of sulfonamide in the blood should be significantly less than that required with each of the other 3 drugs.

No significant effects of the sulfonamides on the average total leukocyte counts were seen, although 2 individuals consistently showed decreased counts following each exposure to a sulfonamide.

Data on the renal elimination of the 4 sulfonamides are presented in Table 2. From these data it is apparent that the percentages of conjugated sulfonamide which appeared in the urine were less with sulfadiazine and sulfathiazole than with either sulfamerazine or sulfamethazine. The greatest percentage of conjugated drug was excreted following sulfamethazine administration. It will be noted (Table 2) that the average percentage of conjugated sulfonamide found in the urine following the administration of a given drug was very constant. These data reflect the remarkable constancy with which each individual conjugated each sulfonamide.

TABLE 2.—AVERAGE SULFONAMIDE CONTENT OF THE URINE, COLLECTED DURING 24-HOUR PERIODS, OF MEN RECEIVING SMALL MAINTENANCE DOSES OF VARIOUS SULFONAMIDES

Drug	Daily maintenance dose (gm.)	Day of dosage	Average amount of free sulfonamide (gm.)	Average amount of conjugated sulfonamide (gm.)	Conjugated sulfonamide (%)
Sulfamerazine	0.5	6	0.21 ±0.06	0.29 ±0.05	57.4 ±11.1
	1.0	5	0.35 ±0.11	0.50 ±0.11	58.8 ±12.4
	1.0	7	0.40 ±0.13	0.50 ±0.12	55.7 ±12.5
Sulfadiazine	1.0	5	0.50 ±0.09	0.25 ±0.07	33.8 ± 6.0
	1.0	7	0.59 ±0.11	0.26 ±0.05	30.5 ± 5.4
Sulfamethazine	1.0	5	0.28 ±0.15	0.64 ±0.17	70.0 ±14.0
	1.0	6	0.28 ±0.16	0.64 ±0.16	69.7 ±17.0
Sulfathiazole	1.0	5	0.63 ±0.10	0.27 ±0.10	27.1 ± 7.3
	1.0	6	0.70 ±0.10	0.25 ±0.10	26.3 ± 5.7

Comment.—The data on renal elimination and concentration in the blood confirm our previous findings[21] in which the absorption of sulfamerazine was shown to be more rapid and more complete, and the excretion by the kidney slower, than that of sulfadiazine. These findings account for the maintenance of a given concentration in the blood with smaller doses of sulfamerazine than with sulfadiazine.

Although with small doses, such as were given in this study, urinary solubility is not a particularly important factor, it may be well to comment on the relative solubilities of these drugs, particularly on the relation between sulfadiazine and sulfamerazine. Gilligan *et al.*[8,9] emphasize the great importance, in the prevention of renal complications, of the maintenance of a neutral or alkaline urine, which enormously increases the solubility of sulfadiazine, sulfamerazine and sulfamethazine, and their acetyl derivatives. In contrast, as is shown in their Table 4, the solubility of sulfapyridine, acetylsulfapyridine or of acetylsulfathiazole is very little increased by alkalinization. The absolute solubilities of sulfadiazine, sulfamerazine and their N_4-acetyl derivatives were found to be somewhat greater in urine[21] than in buffered solutions.[8,9] The solubilities of sulfamerazine and acetylsulfamerazine were somewhat greater than those of sulfadiazine and acetylsulfadiazine, respectively, in urine at acid pH levels. This is of importance since it is at acid pH levels that there is danger of precipitation of the drugs in the urinary tract. Also of significance is the fact that in maintaining a given blood level, larger doses of sulfadiazine, sulfamethazine or sulfathiazole are required than of sulfamerazine and,

therefore, the total amount of drug which must pass through the kidneys each day is appreciably less with sulfamerazine than with any of the other sulfonamides.

The maintenance of equivalent sulfonamide concentrations in the blood, by the administration of sulfamerazine in doses one-half as large as those of sulfadiazine, leads to the appearance in the urine of closely similar amounts of the acetylated derivatives (Table 2). Under these circumstances, however, the danger of crystal formation is appreciably less with sulfamerazine than with sulfadiazine because of the greater solubility of acetylsulfamerazine in urine of normal acidity. Care should of course be taken, when either these or other sulfonamides are used, to prevent the excretion of urine of low volume or of low pH, conditions which favor precipitation in the urinary tract of the acetylated derivatives of all the sulfonamides now available.

The concentration produced in the blood by single daily doses of 0.5 or 1 gm. of sulfamerazine should be of clinical significance. Several investigators have described beneficial effects from the use of small doses of sulfanilamide, given over long periods, in the prophylaxis of streptococcal infection in rheumatic subjects.[2,4,13,14,18,19]

Loveless and Denton[16] used sulfathiazole in the prophylaxis of gonorrhea. The drug was given in doses of 2 gm. to soldiers leaving a post, and, if "station prophylaxis" were not given, an additional 2 gm. was administered on return to camp and 2 gm. the following morning. Unfortunately blood level data were not given. The authors found a marked reduction in the incidence of gonorrhea and of chancroid in the group treated as described, in comparison with a large group of soldiers to whom sulfonamides were not administered.

Recently Watson *et al.*[20] presented convincing evidence of the control of a scarlet fever epidemic, in which several thousand men were given repeated daily 1 gm. doses of sulfadiazine, and among whom only 3 developed any sign of toxicity (rash). In a group of 50 of these men the average and median sulfadiazine concentration, about 6 hours following dosage, was 2.6 mg. per 100 cc. of blood. This agrees well with our observations, made in a smaller group, but at a comparable time and with the same dose, which indicated the presence of about 3.2 mg. of sulfadiazine per 100 cc. of blood. It should be noted that the daily administration of sulfamerazine in doses of only 0.5 gm. results in the maintenance of an average concentration of free sulfonamide in the blood higher than is produced by daily 1 gm. doses of sulfadiazine, sulfamethazine or sulfathiazole.

Sulfamerazine is so rapidly absorbed and slowly excreted, in comparison with other sulfonamides, that smaller daily doses should be given, and at less frequent intervals, in order to maintain adequate prophylactic or therapeutic blood levels. Clinical findings indicate that a total daily dose of 1 gm. to 4 gm. of sulfamerazine may be given on the basis of only 2 or 3, instead of the customary 4 to 6, divided doses daily.

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Summary.—The average sulfonamide concentrations produced in the blood of 8 normal men by daily 1 gm. doses of sulfamerazine, sulfadiazine, sulfamethazine and sulfathiazole are presented (Fig. 1). The concentration in the blood following maintenance doses of sulfamerazine fell from a daily maximal value of about 6.5 to a minimal value of about 3.5 mg. per 100 cc.; with sulfadiazine from about 3.5 to about 1.5; with sulfamethazine from about 4 to less than 1; and with sulfathiazole from about 2 to less than 1 mg. per 100 cc. Sulfamerazine administered in single 0.5 gm. daily doses (Fig. 2) maintained a concentration in the blood which fell gradually from a level of approximately 4 to a level of about 2 mg. per 100 cc.

Emphasis is placed on the rapid absorption and gradual elimination of sulfamerazine, which make possible the maintenance of a concentration in the blood, with single daily doses of only 0.5 to 1 gm., that is probably sufficient for certain chemoprophylactic purposes. The data presented, as well as clinical experience with sulfamerazine, indicate that adequate therapeutic concentrations in the blood should be maintained by the administration of smaller total daily doses than with other sulfonamides; these doses can be given on the basis of only 2 or 3 divided doses daily.

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STUDIES ON BONE MARROW IN VITRO

II. The Effect of Hemoglobin and Red Cell Stromata on Explanted Bone Marrow

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In a previous paper[5] we have reported experiments on rabbits' bone marrow surviving *in vitro*. The fundamental physiologic activities of the organ, such as maturation of the white and red cells and multiplication of their precursors, taking place during the first days of incubation, were described.

After establishing the behavior of the explanted bone marrow in standard medium, the direct effect of certain substances on the surviving and functioning bone marrow was investigated. The cellular composition of the bone marrow surviving in media containing the added respective substances was studied and compared with that of the bone marrow surviving in standard medium.

This report deals with the effect of hemoglobin solutions and suspensions of red cell stromata on the bone marrow surviving *in vitro*.

Material and Methods. The description of the method to maintain bone marrow fragments *in vitro* is given in the first paper of this series.[5]

Solutions of hemoglobin and suspensions of red cell stromata were obtained in the following way: 10 cc. of rabbits' heparinized blood were centrifuged, the plasma withdrawn, and the remaining red cells washed twice with Ringer solution. Then distilled water was added in the proportion 4 to 1 until the solution had become laked. After further centrifugation, a pure supernatant hemoglobin solution was obtained. The sediment, consisting of red cell stromata, was washed several times with Ringer's solution and, after pouring off the supernatant fluid, a volume of Tyrode solution, equal to the sediment, was added and a suspension of stromata was obtained.

One drop of hemoglobin solution, or one drop of the stroma suspension was added to each tube containing the standard medium (3 drops of Tyrode solution, 3 drops of heparinized rabbits' plasma and 1 drop of chick embryonic extract).

A set of 18 tubes was used in each experiment, so that 6 control tubes contained the bone marrow in the standard medium, 6 the added hemoglobin solution and 6 the added suspension of red cell stromata. Altogether, 9 such experiments on bone marrow obtained from 9 rabbits of the age of approximately 6 to 8 weeks were performed. The bone marrow fragments were incubated for 24 hours and 48 hours and were then histologically examined. After fixation in Zenker's fluid the specimens were embedded in celloidin paraffin. Serial sections 4μ thick were made and stained with hematoxylin-eosin and with Giemsa's stain.

Results. *Effect of Hemoglobin Solution on Bone Marrow* in Vitro. After an incubation period of 24 and 48 hours the bone marrow sur-

* Working under the Cancer Laboratories fellowship.

viving *in vitro* in a medium to which hemoglobin solution was added, is well preserved and without signs of degeneration. The surrounding plasma coagulum contains a varying number of polymorphonuclear leukocytes which have migrated from the explant. The explant itself

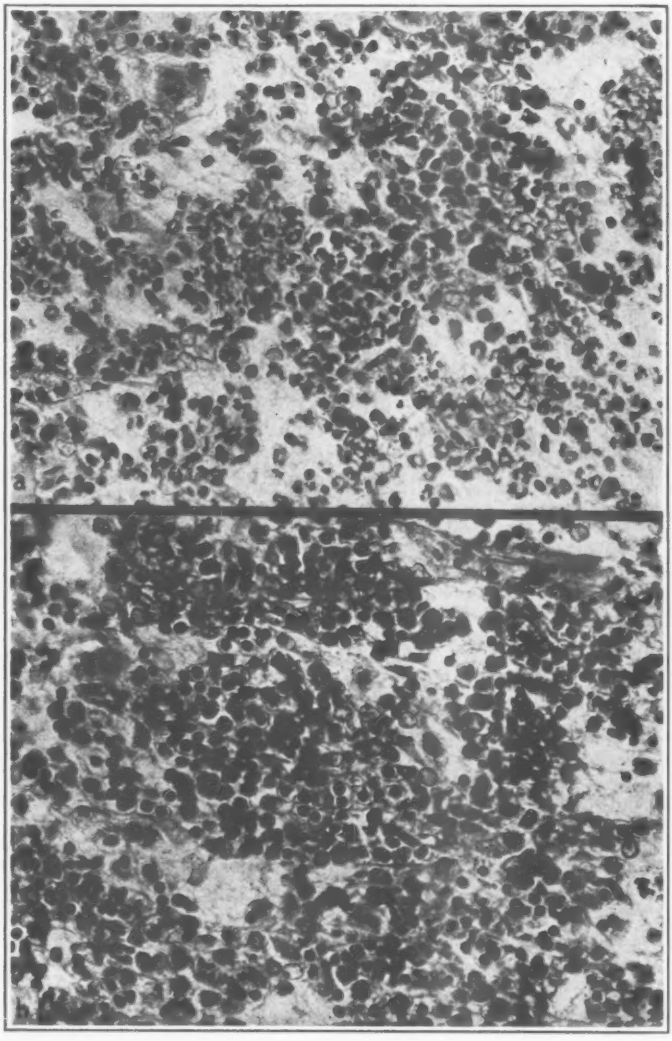

FIG. 1.—Experiment K. 29. Mag. × 500. Hematoxylin-eosin. *a*, Explant of bone marrow in hemoglobin containing medium after 24 hours of incubation. *b*, Explant of bone marrow in stroma containing medium after 24 hours of incubation.

is exceedingly rich in myeloid and erythroid cells. A close inspection reveals an abundance of polymorphonuclear leukocytes which, particularly in the central parts of the fragment, densely fill the trabeculæ and are aggregated in large groups; between them numerous red cells

are also to be found (Figs. 1*a*, 2*a*, 3*a*). Stem cells, myelocytes and nucleated red cells are scattered throughout the central parts of the fragment, and are more concentrated in the peripheral zones. Here numerous immature cells in mitotic division are to be seen.

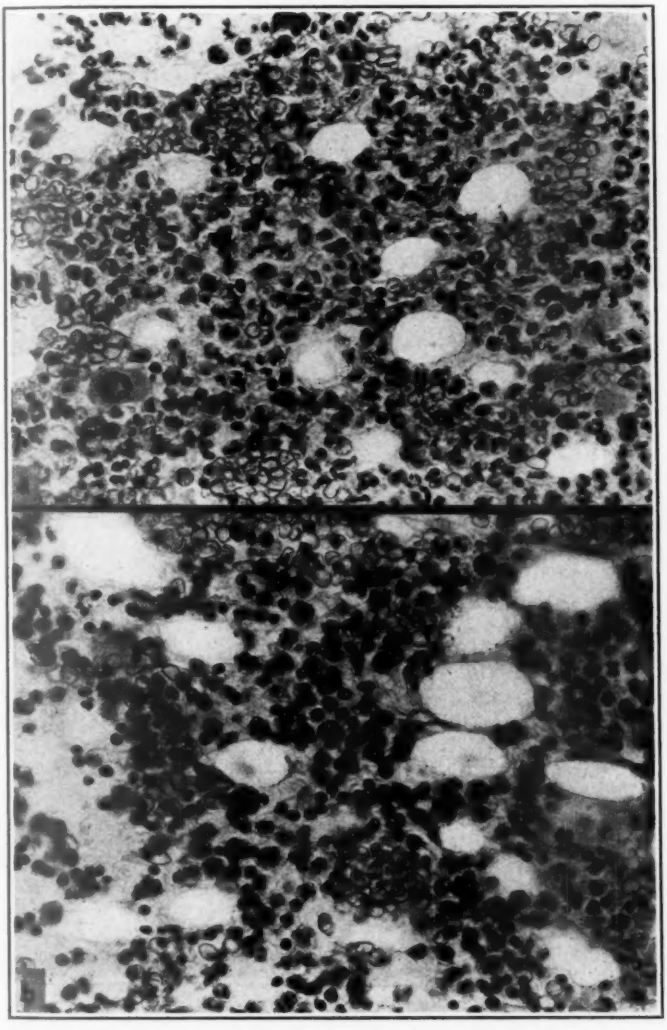

FIG. 2.—Experiment K. 28. Mag. × 500. Hematoxylin-eosin. *a*, Explant of bone marrow in hemoglobin containing medium after 24 hours of incubation. *b*, Explant of bone marrow in stroma containing medium after 24 hours of incubation.

Analyzing the effect of hemoglobin-containing medium on the bone marrow surviving *in vitro*, it is important to remember that, as we have demonstrated in our first paper, the bone marrow culture in the standard medium showed definite signs of maturation and contained a larger number of polymorphonuclear leukocytes and erythrocytes than

the fresh material. Comparison between the explants in hemoglobin-containing medium and those in standard medium after 24 hours of incubation reveals the following results:

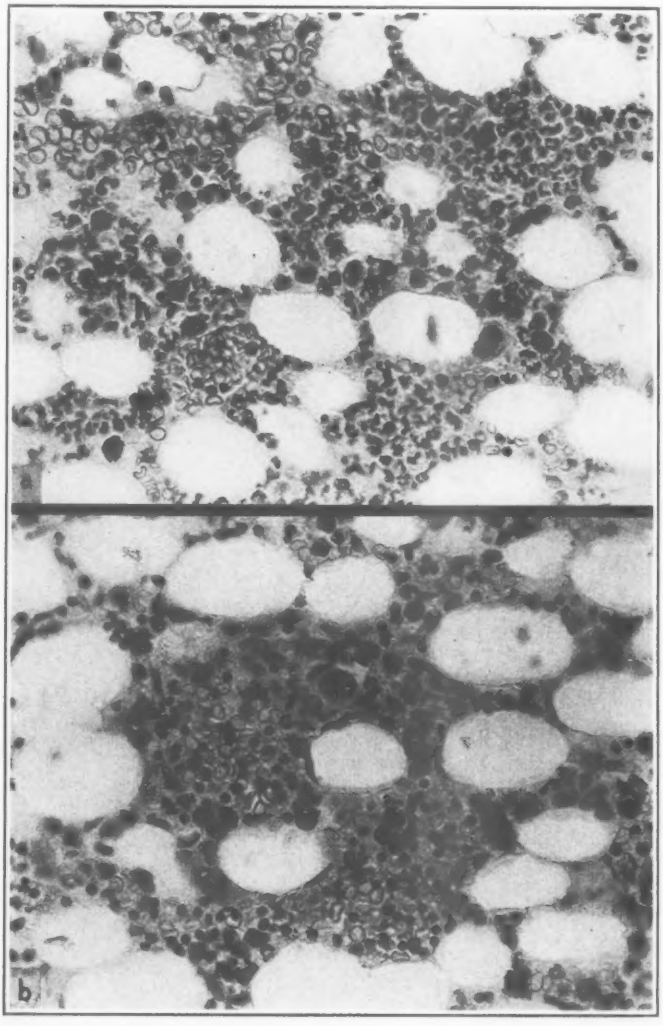

FIG. 3.—Experiment K. 24. Mag. × 500. Hematoxylin-eosin. *a*, Explant of bone marrow in hemoglobin containing medium after 24 hours of incubation. *b*. Explant of bone marrow in stroma containing medium after 24 hours of incubation

The number of polymorphonuclear leukocytes in the explants in hemoglobin-containing medium was in most experiments higher than in the explants in standard medium. The abundance of leukocytes in the experimental fragments was particularly striking in cultures deriving from bone marrow with prevailing leukopoietic activity. In the few experiments on bone marrow with prevailing erythropoietic

activity, the number of leukocytes was low, but relatively higher than in the control fragments. In these instances the predominant cell type were mature red cells.

In order to establish the relationship of the various cell elements in the control and in the experimental bone marrow explants respectively, differential cell counts were made of mature and immature white cells as well as nucleated red cells present in the bone marrow fragments incubated in standard medium and in hemoglobin-containing medium.

TABLE 1.—PERCENTILE INCREASE OF POLYMORPHONUCLEAR LEUKOCYTES IN EXPERIMENTAL FRAGMENTS AS COMPARED WITH CONTROLS

Animal No.		No. of cells counted	Stem cells (%)	Myelocytes (%)	Polymorphonuclear leukocytes (%)	Nucleated red cells	Myeloid: erythroid ratio
R. 24	A	816	1.0	21.3	39.1	38.6	1.6:1
	B	900	0.4	20.9	38.9	39.8	1.5:1
	C	1061	1.8	23.6	18.9	55.7	0.8:1
R. 27	A	815	28.9		42.7	28.4	2.5:1
	B	1299	23.3		49.4	27.3	2.7:1
	C	940	31.7		12.1	56.2	0.8:1
R. 28	A	1584	1.3	10.4	40.7	47.6	1.1:1
	B	1736	1.2	14.4	43.0	41.4	1.4:1
	C	1468	1.7	13.3	15.5	69.5	0.4:1
R. 29	A	873	1.0	20.3	40.2	38.5	1.6:1
	B	1467	0.3	13.1	43.9	42.7	1.3:1
	C	1205	1.1	7.9	24.7	66.3	0.5:1
R. 30	A	1367	20.5		32.5	47.0	1.1:1
	B	1430	14.8		37.9	47.3	1.1:1
	C	1130	20.1		18.0	61.9	0.6:1
R. 32	A	1162	24.1		20.1	55.8	0.8:1
	B	1356	17.5		35.2	47.3	1.1:1
	C	531	18.1		13.9	68.0	0.5:1
R. 33	A	793	18.8		17.4	63.8	0.6:1
	B	946	13.3		25.3	61.4	0.6:1
	C	ca.900	17.3		15.9	66.8	0.5:1
R. 34	A	926	17.9		16.8	65.3	0.5:1
	B	767	17.9		17.7	64.4	0.6:1
	C	576	21.5		12.5	66.0	0.5:1
R. 35	A	591	22.3		26.9	50.8	1.0:1
	B	701	16.5		43.7	39.8	1.5:1
	C	728	17.2		30.1	52.7	0.9:1

A = Section of 24 hours old explants in standard medium.
B = Section of 24 hours old explants in standard medium with addition of hemoglobin solution.
C = Section of 24 hours old explants in standard medium with addition of stroma suspension.

Table 1 shows that there was a marked percentile increase of polymorphonuclear leukocytes in the experimental fragments as compared with the controls, in 6 out of 9 experiments, the average increase being 9.3%. In 1 case they were only slightly increased, in 2 cases the number of polymorphonuclear leukocytes remained the same. The relative

increase of the polymorphonuclear leukocytes was usually higher when originally the absolute number of leukocytes was low.

A corresponding percentile decrease of stem cells and myelocytes in the experimental fragments compared with the control fragments was found in 6 out of 9 experiments. In 2 cases in which the number of polymorphonuclear leukocytes in the experimental fragments remained the same as in the control fragments, the number of stem cells and myelocytes was also the same, and in 1 case there was a slight increase in the experimental fragments.

The percentage of nucleated red cells was practically the same in the experimental as in the control fragments in 4 out of 9 cases. In 4 cases the experimental fragments contained a somewhat lesser number of nucleated red cells, and in 1 case there was a slight increase in the experimental fragments.

Table 1 shows also that the myeloid-erythroid ratio in the experimental fragments remained the same as in the control fragments in 5 out of 9 experiments, was shifted in favor of the myeloid elements in 3 cases, and was only slightly shifted in favor of the erythroid elements in 1 case.

The results of these counts indicate that the addition of hemoglobin produced an increased rate of maturation of polymorphonuclear leukocytes in most experiments as compared with the explants in standard medium. Apart from the increased maturation, multiplication evidenced by mitotic activity was also noted in the experimental fragments. The rate of multiplication, however, was usually somewhat less than in the control fragments. The number of mitoses counted in the respective bone marrow fragments is given in Table 2.

TABLE 2.—EFFECT OF RED CELL STROMATA ON BONE MARROW IN VITRO

Animal No.		No. of mitoses in 10 high-power fields	Animal No.		No. of mitoses in 10 high-power fields
R. 24	A	7	R. 35	A	7
	B	5		B	7
	C	9		C	13
R. 27	A	4	R. 32	A	12
	B	5		B	7
	C	10		C	10
R. 28	A	8	R. 33	A	5
	B	6		B	3
	C	14		C	6
R. 29	A	17	R. 34	A	9
	B	11		B	10
	C	19		C	12
R. 30	A	12			
	B	11			
	C	11			

A = Section of 24 hours old explant in standard medium.
B = Section of 24 hours old explant in standard medium with addition of hemoglobin solution.
C = Section of 24 hours old explant in standard medium with addition of stroma suspension.

Effect of Red Cell Stromata on Bone Marrow in vitro. The bone marrow explants in media to which a suspension of red cell stromata was added, exhibit quite a different picture than the explants in hemoglobin-containing and in standard medium. The outstanding feature of these explants after 24 hours of incubation is the scarcity of polymorphonuclear leukocytes. A further characteristic of the stroma-containing cultures is the prevalence of immature cells, particularly of the red variety.

Erythroblasts, normoblasts, and in a lesser degree stem cells, and myelocytes, fill the stroma meshes throughout the entire pieces (Figs. 1*b*, 2*b*, 3*b*). Besides there are numerous erythrocytes sometimes accumulated in certain regions and forming lakes.

Another typical feature of these cultures is the particularly high number of mitoses in the precursors.

The comparison of the bone marrow pattern of fragments in stroma-containing medium with that of fragments in standard medium reveals the constant and definite reduction of the number of polymorphonuclear leukocytes in the experimental fragments compared with the control fragments. This difference was particularly striking in experiments on bone marrow with prevailing leukopoietic activity, but also seen to a lesser degree in the experiments on bone marrow with prevailing erythropoietic activity.

With the reduction of the polymorphonuclear leukocytes a marked increase of the nucleated red cells in the experimental fragments was noted, as compared with the control fragments.

The percentile numbers of the different cell types given in Table 1 show the changes which have taken place in the experimental fragments in comparison with the control fragments.

Table 1 shows that there is a reduction of polymorphonuclear leukocytes in the experimental fragments as compared with the control fragments in 7 out of 9 experiments, the average reduction being 16.9%. In 1 case they remained practically the same and in 1 case there was a slight increase in the experimental fragments. The percentage of nucleated red cells was clearly augmented in 6 out of 9 cases, the average increase being 20.3%. In the other 3 cases the increase was very small, reaching only an average of 1.9%. In 2 of these cases there was already an abundance of nucleated red cells in the control fragments, these deriving from erythropoietic bone marrow.

The number of stem cells and myelocytes was in 4 out of 9 cases slightly increased in the experimental fragments, in 2 cases practically the same as in the control fragments, and in 3 cases it was somewhat decreased.

It is clearly seen that in the experimental fragments the myeloid-erythroid ratio is definitely shifted in favor of the erythroid elements in 6 out of 9 cases in comparison with the control fragments. From the 3 cases where the myeloid-erythroid ratio remained unchanged, 2 cases were experiments on erythropoietic bone marrow in which the number of nucleated red cells was already very high in the original bone marrow.

Judging from the reduced number of polymorphonuclear leukocytes in the experimental fragments it must be concluded that the addition of red cell stromata rather inhibits white cell maturation. On the other hand, the prevalence of precursors indicates that an increased rate of multiplication has taken place. This is manifested by an increased number of mitoses in the experimental fragments which was found in 7 out of 9 experiments (Table 2).

Table 2 shows that the highest number of mitoses was counted in the fragments surviving in the stroma-containing medium.

Discussion. The effect of the individual components of the red cell on hemopoiesis was the subject of study of many investigators.

The direct effect of hemoglobin on bone marrow cultures was briefly described by Jeney,[1] who claimed to have observed a stimulating effect on hemopoiesis, manifested by an increased number of nucleated red cells. As far as we know, no experiments with the addition of red cell matrix to bone marrow cultures have been performed.

Experiments on animals concerning the effect of hemoglobin on the bone marrow have been registered by McMaster and Haessler[2] and by Miller and Rhoads.[3] The former authors found an increase of the hematopoietic tissue and especially of the erythropoietic islands in bone marrow of rabbits rendered anemic by repeated bleedings in which the blood loss was replaced by injections of hemoglobin. Miller and Rhoads, using the same technique, found likewise erythroblastic hyperplasia, but with the appearance of megaloblasts in the bone marrow of the injected animals.

No data in the literature are available concerning the effect of the red cell stromata on the bone marrow *in vivo*.

The effect of injected hemoglobin on blood regeneration has been extensively studied by Whipple and co-workers.[7] These authors found that, if a stroma-free solution of hemoglobin was administered intravenously or intraperitoneally to dogs rendered anemic by repeated bleedings, 80 to 90% of the hemoglobin injected was recovered in newly formed cells. Robscheit-Robbins[6] assumed that hemoglobin breakdown products are direct irritants to the bone marrow as well as building stones.

The effect of red cell stromata on blood regeneration was investigated by Ono.[4] According to this author the intravenous injection of red cell stromata in quantities corresponding approximately to the daily red cell destruction, produced an increase of hemopoiesis in rabbits.

The experiments described in this paper indicate that there is a distinct difference in the response of the bone marrow surviving *in vitro* to hemoglobin and red cell stroma. The addition of hemoglobin to the standard medium resulted in an increase in the number of mature cells. The effect of stroma, on the other hand, was characterized by an increased number of immature cells, mainly red cells precursors, and reduction of mature white cells. Both components of the erythrocyte had thus a stimulating effect on the bone marrow *in vitro*. The stimulation caused by hemoglobin was manifested mainly in the direction of maturation, while the effect of stroma was seen in the direction

of multiplication—particularly of the erythroid elements, thus producing *in vitro* an erythroblastic bone marrow.

Summary. A different and characteristic response of explanted bone marrow to both components of the erythrocyte was found.

The addition of hemoglobin resulted in an increased rate of maturation of white and red blood cells.

The addition of red cell stromata, on the other hand, produced an increased rate of multiplication, particularly of the red cell precursors.

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CARDIAC ARRHYTHMIAS IN 1000 CASES OF PULMONARY TUBERCULOSIS

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The evaluation of the clinical significance of cardiac arrhythmias encountered in cases of pulmonary disease requires the consideration of the anatomically adjacent extracardiac factors. Otherwise, their significance is that of arrhythmias in general. They very frequently occur in the absence of cardiac disease. At times, however, they constitute the sole evidence of severe myocardial embarrassment. Their presence in cases of pulmonary disease may be purely accidental. One is justified, however, in correlating their occurrence with existing extracardiac factors and in considering in some cases the probability of an etiologic dependence. Such consideration may give the existing arrhythmia a special function—that of an indicator that pathophysiologic activities originating in the pleuro-pulmonary apparatus have invaded the heart. The clinician, naturally, may be influenced in his prognosis and therapeutic approach by the consideration of this etiologic dependence.

In cases of pulmonary tuberculosis the extracardiac factors in the causation of abnormal cardiac rhythm may be one or a combination of several of the following: (1) The influence of the tuberculous process on the intravascular pulmonary tension. (2) The anatomic involvement of the pericardium and myocardium in the process consuming the adjacent pulmonary tissue. (3) The toxic influence of the disease on the heart muscle and the conduction system. (4) The mechanical

involvement of the heart and the great vessels in mediastinal torsion and displacement. (5) Reflexes initiated in the disturbed anatomy and physiology of the respiratory apparatus without the mechanical involvement of the heart and great vessels.

An attempt to evaluate some of these factors is the purpose of the present report.

Material and Results.—The electrocardiograms of 1000 consecutive cases with evidence of chest tuberculosis admitted to Sea View Hospital were reviewed with particular reference to the incidence and type of arrhythmias encountered. There were 78 cases presenting arrhythmias (Table 1). Twelve cases showed sinus arrhythmia; 22 presented premature auricular contractions and premature ventricular contractions; 14 cases presented various types of auriculoventricular conduction impairment, mostly first stage heart block; 20 cases presented intraventricular conduction impairment; 10 cases presented miscellaneous arrhythmias which included: sinus block, 1 case; sinus arrhythmia with paroxysmal nodal rhythm, 1 case; sinus bradycardia, 1 case; auricular fibrillation, 3 cases; auricular tachycardia, 2 cases; auricular flutter, 1 case; premature auricular and ventricular contractions with paroxysmal auricular tachycardia, 1 case.

TABLE 1.—TYPE OF ARRHYTHMIA IN RELATION TO AGE AND CARDIAC DISEASE

	Age (yrs.)			Cardiac disease	
Arrhythmia:	15 to 49 (incl.)	50 and over	Total	Present	Absent
Sinus arrhythmia	11	1	12	1	11
Premature contractions	11	11	22	13	9
Delayed auriculoventricular conduction time	10	4	14	11	3
Delayed intraventricular conduction time	6	14	20	19	1
Miscellaneous	3	7	10	9	1
Total	..	..	..	53	25

The cases with intraventricular conduction impairment were included, as they frequently are, in the classification of cardiac arrhythmias, although, strictly speaking, they are rhythmic arrhythmias.

When the arrhythmias were tabulated in relation to the activity of the pulmonary process (Table 2) as evidenced by positive sputum, elevated temperature, and increased sedimentation rate, it was noted that there were 4 times as many cases of arrhythmias in the active group as in the inactive group. However, the observation is without significance, as the Sea View Hospital population is made up of about 4 times as many active as inactive cases.

When the arrhythmias are tabulated in relation to the site, type, and extent of the pulmonary lesions (Table 3), a fact which may have some significance becomes prominent, namely, that arrhythmias are more frequently associated with right-sided than with left-sided lesions. The great vessels and nerve structures are more exposed on the right side than on the left; possibly their distortion is at least reflexly responsible for the abnormal cardiac manifestations.

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Table 1 presents the arrhythmias in relation to age and cardiac disease. With one exception the sinus arrhythmias occurred in the younger age group, and with one exception no evidence of cardiac disease was obtained in this arrhythmia group. Premature contractions were equally divided between the 2 age groups. The majority of them had evidences of cardiac disease. The miscellaneous arrhythmias had evidences of cardiac disease in all but one case, and the majority of them occurred in the older age group. The intraventricular and the auriculoventricular conduction impairment group was also predominantly associated with evidences of cardiac disease.

The evidence of cardiac disease consisted of objective criteria, namely, a history of syphilis or polyarticular rheumatism; physical findings such as peripheral sclerosis or unmistakable cardiac murmurs indicative of mitral or aortic disease; fluoroscopic and Roentgen ray evidences of enlargement of the heart and aorta; and typical electrocardiographic changes indicative of coronary artery occlusion.

Comment.—We are not aware of any statistical information on cardiac arrhythmias comparable with the type of material in Sea View Hospital. This institution is one of the few places in the United States where routine electrocardiograms are taken on admission of every case. The statistics available, such as those of White and Jones,[5] are based on electrocardiograms taken of patients with cardiac symptoms. To compare our figures with this group will not be instructive.

To the best of our knowledge there is only one fairly large series of cases of pulmonary tuberculosis with electrocardiographic studies reported, the one by Leverton.[3] While this author does not specifically discuss cardiac arrhythmias, he observed intraventricular impairment in 7.2% of his cases as compared with our 2%. The average age of his group was 39.4 years and only 6 out of 30 cases had clinical or postmortem evidence of coronary sclerosis. It is his opinion that a nutritional disturbance of the myocardium occurs in pulmonary tuberculosis of long standing which may produce an electrocardiographic picture similar to that found in coronary sclerosis. Apparently, this contention is not borne out by our findings. Our study seems to indicate that the abnormalities in question are a manifestation of intrinsic cardiac disease and are related to the age group with vascular degenerative changes.

TABLE 2.—RELATION OF ARRHYTHMIA TO ACTIVITY OF TUBERCULOSIS

	Inactive	Active	Tota
Arrhythmia:			
Sinus arrhythmia	5	7	12
Premature contractions	2	20	22
Delayed auriculoventricular conduction time	3	11	14
Delayed intraventricular conduction time	4	16	20
Miscellaneous	2	8	10
Total	16	62	

Auriculoventricular block in our series occurred predominantly in the younger age group. In only 3 cases, however, were no evidences of cardiac involvement present, other than the abnormal electrocardio-

gram. Of these 3 cases, one was 48 years old, one 18 years old, and one 32 years old. All 3 had considerable mediastinal shift. There is a possibility that in some cases mediastinal displacement can alter the configuration of the P wave so as to make it measurably consistent with the picture of first stage heart block.[2] This may possibly explain such reports as the one by Pastore.[4] He observed a considerable number of cases of auriculoventricular block in tubercular children without evidences of rheumatic fever. However, it is possible that in a small number of cases toxic influences of the tuberculous process may also play a rôle in the causation of conduction difficulties.

TABLE 3.—ARRHYTHMIAS IN RELATION TO PULMONARY LESIONS

	Type of arrhythmia					
	Sinus arrhythmia	Premature contractions	Delayed auriculo-ventricular conduction time	Delayed intra-ventricular conduction time	Miscellaneous	Total
Number of cases	12	22	14	20	10	78
Intrathoracic lesions	1	1	0	1	0	3
Exudative productive lesions:						
Unilateral (right)	1	0	1	1	0	3
Unilateral (left)	0	0	0	1	0	1
Bilateral:						
Predominant on right	1	0	0	0	1	2
Predominant on left	2	0	0	0	0	2
Caseous pneumonic lesions:						
Unilateral (right)	2	3	1	3	0	9
Unilateral (left)	0	0	0	0	0	0
Bilateral:						
Predominant on right	1	9	2	4	4	20
Predominant on left	3	4	3	1	1	12
Fibrotic lesions:						
Unilateral (right)	0	0	0	0	1	1
Unilateral (left)	0	0	0	0	0	0
Bilateral:						
Predominant on right	0	1	1	3	0	5
Predominant on left	0	0	2	0	0	2
Lesions equal bilaterally	1	4	4	6	3	18
Predominant lesions:						
Right	5	13	5	11	5	39
Left	5	4	5	2	2	18
Tracheal and mediastinal displacement:						
Right	6	6	7	11	4	34
Left	0	2	2	1	2	7
Effusion pneumothorax hydropnx.:						
Right	3	3	2	6	3	17
Left	4	4	3	2	1	14

The effect of mediastinal displacement on the irritability of the myocardium has been stressed by a number of foreign writers and in this country by Brumfiel.[1] Of the 15 cases of mediastinal distortion studied by Brumfiel, 7 presented extrasystoles. While it is possible that a large number of the 1000 cases we studied had extrasystoles at some time, only 2.2% (22 cases) had premature contractions recorded in their admission electrocardiograms. Of these, 13 had evidences of intrinsic cardiac disease, and only 9 cases presented no such evidence, an incidence of about 1% in the entire group studied. This incidence is hardly significant when compared with the frequency of mediastinal

distortion seen at Sea View Hospital, as evidenced by Roentgen ray findings and the electrocardiographic abnormalities expressed in the directional changes of the QRS complex and T wave.

While the evidence points to the presence of intrinsic cardiac disease as an etiologic factor in producing arrhythmias, the findings in Table 3 are suggestive that extracardiac factors may play a rôle in precipitating the appearance of such arrhythmias. It is conceivable that in cases with mediastinal torsion the relationship and course of the cardiac nerves are likewise disturbed, and this may be responsible for the increased irritability of the myocardium. The structural arrangement of the right mediastinum may possibly supply the anatomic basis for the pathophysiologic changes. The predominance of right-sided lesions in the arrhythmia group is apparently not a reflection of case distribution in general. Out of 300 consecutive admissions reviewed with particular reference to this point, the number of cases with predominant right-sided lesions was about equal to the number of cases with predominant lesions on the left side.

Conclusion.—1. Pulmonary tuberculosis does not affect the incidence of abnormal cardiac rhythm or abnormalities in the conduction mechanism. In the majority of cases presenting these abnormalities, other clinical or laboratory evidence of intrinsic cardiovascular involvement can be elicited.

2. It is suggested that right pulmonary lesions involving the mediastinum may constitute an extracardiac factor in the causation of arrhythmias and conduction abnormalities in a *previously* diseased myocardium.

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THE SIGNIFICANCE OF MARKED LEFT AXIS DEVIATION OF THE ELECTROCARDIOGRAM*

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While it is generally recognized that moderate deviation of the electrical axis of the heart to the left is a common finding in normal individuals, its frequency approximating 20%, there appears to be

* This paper is based on work carried out in 1937–38 at the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

little agreement as to the significance of the less frequent but by no means rare pattern of marked left axis deviation in which S_2 is of greater amplitude than R_2 (Fig. 1). References to this electrocardiographic pattern are few and opinions as to its significance are contradictory. Cohn[1] reported finding it once in a series of 218 normal soldiers.

Katz[3] interprets this type of record as definitely abnormal, indicating left ventricular preponderance. Master[4] has published a record of this type in a woman of 75 and described it as follows: "The electrocardiogram indicates the left ventricular hypertrophy by left axis deviation. It is otherwise normal." However, on the opposite page referring to

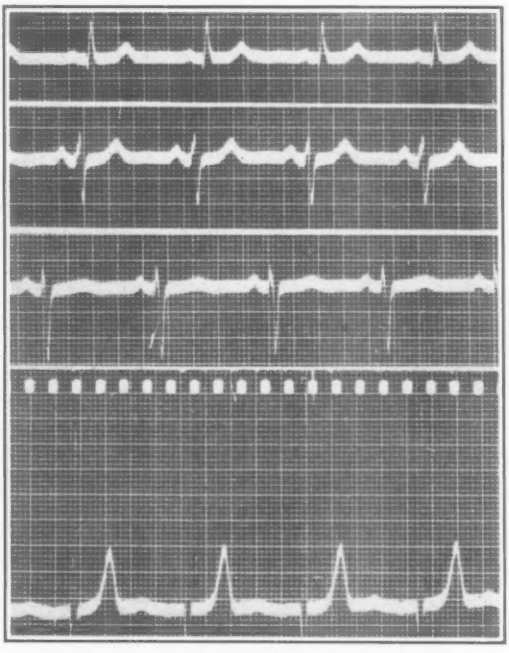

FIG. 1.—Pattern of marked left axis deviation.

the same record, he writes: "Electrocardiogram is negative. The left axis deviation is normal at this age." In the absence of any large scale study of the clinical and pathologic findings associated with the pattern under discussion it has been difficult to form an opinion as to its meaning.

In order to assess the significance of marked left axis deviation the clinical records of 200 consecutive cases exhibiting the pattern were studied. One hundred of these cases exhibited an upright T_3 and 100 exhibited an inverted T_3.

To make a crude estimate of the relationship between predominant left-sided enlargement and the pattern under consideration, the cases were divided into 2 groups, based upon the clinical findings. In one

group were placed all the cases in which factors were present which might be expected to produce left ventricular enlargement—such as arterial hypertension or valvular disease. Hypertension was defined as a systolic blood pressure above 150 mg. Hg or a diastolic blood pressure above 90 mg. Hg. In this group were also included all cases exhibiting cardiac enlargement by Roentgen ray even if neither of the above etiologic factors were known to be present. In the second group were placed all cases with normal blood pressures, without valvular disease or in which the total transverse diameter of the heart as measured by Roentgen ray was less than one-half of the internal diameter of the thorax. It is clear that the criteria employed would not accurately separate all the cases of left ventricular enlargement from those with normal hearts, but there would be some error in both directions which would cancel out to a certain extent in such a large group. These figures indicate that 103 cases (51.5%) showed no obvious cause for or (when measured) positive Roentgen ray evidence of enlargement of the heart.

Measurements of the heart were made from teleroentgenograms in 97 cases and in 35 cases (37%) the cardiothoracic ratio was less than 50%.

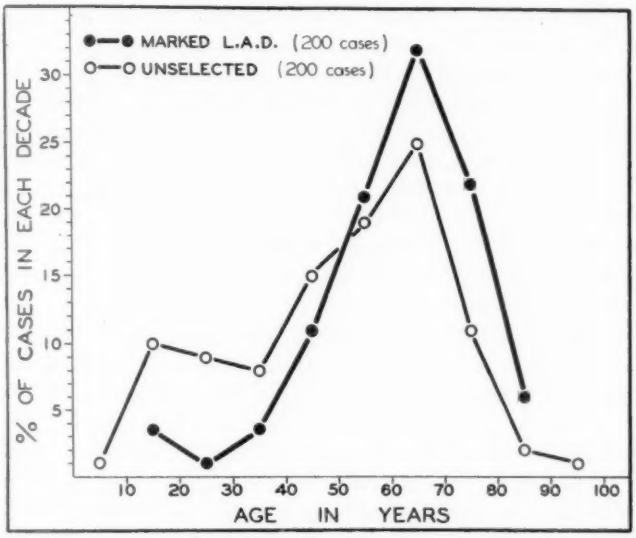

FIG. 2.—Age incidence of 200 cases exhibiting marked left axis deviation as compared to 200 unselected cases from the electrocardiographic laboratory. Note increased incidence in older decades.

A comparison of the age incidence of these 200 patients with marked left axis deviation with the age of 500 unselected cases from the electrocardiographic file showed a distinctly increased frequency of the condition in the older age groups (Fig. 2). A single chest lead (Lead IVF or IVR) was taken in each case and was normal in 186, abnormal in 14. These findings would suggest that the pattern of marked left axis deviation would not in itself alter the contour of the chest lead to an

abnormal degree such as is seen associated with the pattern of left ventricular enlargement.

The autopsy records of 27 cases were analyzed. The actual heart weights were as follows (italics indicate females): *700*, 650, 640, 640, *600*, 580, 540, 500, *500*, *465*, 450, 450, 420, 420, 420, *420*, *400*, 390, 340, 330, *310*, *310*, 300, 280, 275, 270, *250*. Ten of the hearts were of normal weight (below 400 gm. for men and 350 gm. for women). Coronary arteriosclerosis with slight or greater degrees of narrowing was present in 9 cases. One case exhibited complete occlusion of the descending branch of the left coronary artery with myocardial infarction. Myocardial fibrosis of greater or less degree was recorded in 12 cases and was absent in 13. It was not recorded in 2. Valvular disease was noted in 8 cases, 4 of aortic stenosis, 2 of aortic insufficiency and 2 of mitral stenosis.

Complete absence of any evidence of organic disease of the heart was recorded in 8 cases (30%).

Discussion. Deviation of the electrical axis to the left may be caused by any one of 4 factors, namely: 1. *Enlargement of the left ventricle.* In order to make a positive interpretation of left ventricular enlargement there must be certain changes in Lead I consisting primarily of a depression of the S–T interval and in more advanced cases by frank inversion of T_1, with concomitant changes in the opposite direction in Lead III. Not invariably present but of positive significance if found, is an increase in voltage of R_1. The actual deviation of the axis may be slight or, in vertically placed hearts, even absent. This pattern may develop even before there is detectable Roentgen ray evidence of enlargement.[2] Records of this type were excluded by the criteria employed.

2. *Delayed activation of the left ventricle,* easily recognized by the prolongation of the Q–S interval. Records of this type were also excluded by the criteria employed.

3. *Transverse position of the heart.* This is the most frequent cause of left axis deviation being found in individuals of stocky build or with high diaphragm from obesity, pregnancy, etc. It is due to rotation of the heart to the left on its A–P axis and may be recognized by a tendency to inversion of all the complexes in the third lead—P-waves and T-waves as well as the initial ventricular complex. Seldom if ever, does elevation of the diaphragm cause the marked degree of left axis deviation which is the object of this discussion. Although it was doubtless a contributing factor in some cases, the Roentgen ray studies did not reveal an abnormal frequency of transverse position of the heart in this series.

4. *Rotation of the heart to the right on its longitudinal axis.* This is the phenomenon which causes the paradoxical shift in the electrical axis to the left when a person lies on his right side. The effect of this rotation is to swing the left ventricle from a relatively posterior position in relation to the right ventricle into a position which is relatively less posterior and more lateral. Since the muscle mass of the left ventricle normally far exceeds that of the right ventricle, a slight degree of rota-

tion on the long axis would be expected to exert a marked effect on the electrical axis. This was clearly demonstrated on dogs by Meek and Wilson,[5] who rotated the heart *in situ* by means of sutures attached to the epicardium. In man, rotation of the heart on its long axis might occur as the result of a congenital variation, a change in the shape of the thorax, displacement of the mediastinum by air, fluid or massive collapse of the lung, pleuro-pericardial adhesions, and by left ventricular enlargement. The degree of rotation necessary to produce a marked shift in electrical axis to the left may be so slight as to escape routine Roentgen ray or postmortem observation and it was not recorded in any of the cases in this series. In only a relatively small number of the cases were gross factors other than left ventricular enlargement noted which might explain rotation. The tendency of the axis to shift to the left with increasing age which has been described by Schlomka[6] and confirmed by the present study could be ascribed to senile changes in the shape of the thorax with resultant rotation of the heart. In brief, the relationship of marked left axis deviation to rotation of the heart on its longitudinal axis remains a tenable but entirely unproved hypothesis, and whatever the explanation for this electrocardiographic variant may be, the fact stands out that a high percentage of the hearts which exhibit it are entirely normal in every respect. The figures are particularly significant because they come from a charity hospital where electrocardiograms are not taken as a routine but only if heart disease is suspected. In other words, this study is based on a group which has already been selected on the basis of suspected heart disease and which therefore is heavily weighted in that direction, so that the finding of as many as 30% *entirely* normal hearts at autopsy would indicate that marked left axis deviation is of no specific pathologic significance.

Summary. An attempt was made to correlate marked left axis deviation of the electrocardiogram with significant clinical and postmortem findings. A study of the clinical records in 200 cases revealed that 51.5% had no underlying reason for or evidence of, left ventricular enlargement.

Measurements of the heart from teleroentgenograms in 97 cases were within normal limits in 35 cases (37%).

In 27 autopsied cases the heart was entirely normal anatomically in 8 (30%). There was a definite increase in the incidence of the pattern in the older age groups.

Conclusion. The finding of marked left axis deviation in an otherwise normal electrocardiogram is to be regarded as a normal variation which, though encountered with increasing frequency with advancing age, cannot be correlated with ventricular enlargement, coronary disease or myocardial disese.

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DEVELOPMENT OF HYPERTENSION ASSOCIATED WITH LESIONS OF THE KIDNEY

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The thought that renal disease is associated with an elevated blood pressure was initiated by Richard Bright more than a century ago. Subsequently, another interpretation of the cause for a rise of arterial tension was made by various clinicians in Germany, England, France, and the United States. Their ideas may be gathered from the terms they applied to hypertensive disease:

"Latent arteriosclerosis"—von Basch 1876;
"Pre-albuminuric stage of Bright's disease"—Mahomed 1879;
"Pre-sclerosis"—Huchard 1893;
"Hyperpiesis"—Allbutt 1895;
"Essential hypertension"—Frank 1911;
"Hypertensive cardiovascular disease"—Janeway 1913;
"Malignant hypertension"—Keith, Wagener and Kernohan 1928.

A reversal of opinion came about in 1934 when Goldblatt and his colleagues published the results of their observations.[2] From their classical experiments which demonstrated that renal ischemia will cause a rise in blood pressure, they endeavored to establish a unitarian etiology for hypertension, namely, a functional derangement of kidney activity resting upon a morphologic basis.[3]

The efforts of Homer Smith,[5] either through his own experiments or the application by others of methods devised by him, proved that in many cases of hypertension, not only is renal function normal but the flow of blood through the kidneys is not diminished. Definite evidence that hypertension is not necessarily secondary to renal disease was furnished by Castleman and Smithwick.[1] They investigated kidney biopsy material obtained at subtotal sympathectomy operations and discovered a considerable number of normal kidneys, both on gross inspection and on microscopic examination, in hypertensive patients. Thus the concept of primary, or essential, hypertension may be considered as definitely reëstablished.

This does not imply that hypertensive states cannot be secondary to kidney disease. In chronic albuminuria due to nephritis, we have found that hypertension is more frequently developed as a serious complication than is renal insufficiency.[4] Many reports have given enthusiastic accounts of cures of hypertension by unilateral nephrectomy. More recently, considerable skepticism on this score has arisen. Both urologists and pathologists have published a great deal of material showing that there are as many persons with lesions in the urinary tract who have hypertension, as persons without hypertension who have corresponding renal involvements. The climax of this situation is the conclusion of Homer Smith and his associates,[5] that data from the literature are impressive in their statistical demonstration that unilateral renal disease and surgical lesions of the urinary tract do not predispose to hypertension.

The observation of a number of cases over a period of years, I believe, enables us to clarify this problem. It would appear that at the onset and during the earlier stages of any renal lesion there may be no rise in blood pressure, but as the involvement persists and progresses, there comes a time when intermittent elevations of blood pressure occur and, finally, the hypertension becomes permanently established. The reason for this is probably that both the pressor and antipressor substances generated by the diseased as well as the normal kidney, compensate for one another up to a certain point until those factors which increase the blood pressure dominate the picture, at first intermittently and, later, constantly. Numerous cases can be cited that demonstrate the individual phases of this whole series of events. However, one case that gives the complete picture furnishes satisfactory evidence, and is fairly conclusive in regard to the validity of these statements is represented by the data given in Table 1.

TABLE 1.—J. K., F., 31 (1935)

Date		Blood pressure	
		Systolic	Diastolic
1935	Feb. 25	176	104
	June 22	152	94
	July 23	136	94
1936	Feb. 25	156	94
1938	Oct. 17	164	94
	29	164	104
1939	May 18	138	88
	Oct. 31	154	94
1940	June 15	186	116
	July 15	196	118
	29	132	76
	Oct. 4	162	96
	26	142	94
1941	Jan. 4	176	106
	16	202	126
	18	172	98
	Feb. 13	198	116
	18	Right nephrectomy	
	Apr. 3	134	88
	June 4	142	86
	July 11	136	86
	Sept. 9	136	84
	12	124	76
	30	152	104
	Oct. 1	114	76
1942	Jan. 3	132	82
	Feb. 12	124	80
	Apr. 14	118	82
	July 17	128	80
	Oct. 10	136	90
	Dec. 29	132	88
1943	April 17	112	78
	July 22	124	84
	Sept. 25	136	86

Intermittent hypertension changing to persistent hypertension in 6 years. Return of blood pressure to normal after removal of an atrophic, functionless kidney caused by an aberrant vessel compressing the uretero-pelvic junction.

Case Study. This patient had a congenital obstruction at the right ureteropelvic junction resulting from an aberrant vessel. From 1935, when she was 31 years old, to 1941, there was an intermittent rise in blood pressure to which

no detailed attention was paid largely because of the unwillingness of the patient to coöperate, and also for the reason that there were intervals when the blood pressure was at an approximately normal level. In 1941 the blood pressure became permanently elevated and it was at this time that a complete urologic examination was done; and a functionless right kidney demonstrated. Right nephrectomy showed that the kidney had been destroyed because of an aberrant vessel compressing the ureter at the uretero-pelvic junction. For a period of 2½ years following the nephrectomy the blood pressure dropped and remained at almost normal levels.

It is evident from these observations that a human being can carry a unilateral lesion in the kidney for 37 years, or perhaps longer before hypertension becomes permanent. The fact that the blood pressure maintained a much lower level for the observed period of 2½ years after the atrophic kidney had been removed, demonstrates that this diseased kidney had been responsible for the production of the elevated blood pressure.

Conclusions. Unilateral renal disease may exist for many years without affecting the blood pressure. As compensatory processes for the maintenance of normal arterial tension became strained, periods of intermittent rise in blood pressure occur. Finally, a permanent hypertension may develop. The extirpation of a unilaterally diseased kidney should prevent a rise in blood pressure, or remedy it if it has become permanently established, provided there are no causes for hypertension either in the remaining kidney or elsewhere in the body.

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STUDIES ON THE MORPHOLOGY OF THE ADRENAL CORTEX AND ON THE EXCRETION OF 17-KETOSTEROIDS IN HYPERTENSIVE PATIENTS

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It is well known that impaired function of the adrenal cortex is associated with hypotension. Conversely, neoplasm of the adrenal cortex is generally accompanied by hypertension; the elevated blood pressure frequently returns to normal after the offending tumor is removed.[2] Likewise, excessive administration of desoxycorticosterone

acetate may cause hypertension in patients with Addison's disease,[9,18,20,31,34] in adrenalectomized animals,[32] in normal animals[3,14,17,27,32] and in hypertensive animals.[27] The production of experimental hypertension by compression of the renal artery is impossible in adrenalectomized dogs and adrenalectomy is followed by a prompt fall in the blood pressure of dogs previously made hypertensive by clamping the renal artery.[1,7,13,24]

At autopsy, the adrenal glands of hypertensive patients are said to reveal hyperplastic or adenomatous changes in the cortex,[21,22,23,26] the incidence of such morphologic changes being greater than could be accounted for by the factor of age alone.[19,23] Yet the actual rôle which the adrenal cortex plays in the maintenance of the blood pressure in patients with "essential" hypertension remains obscure.

In the present study, the incidence of morphologic changes in the adrenal cortex of patients with "essential" hypertension was reinvestigated. This was prompted particularly in view of a recent report[8] which maintained that hypertensives demonstrate no greater incidence of histologic alteration in the adrenal cortex than do subjects with normal blood pressure. In addition, the excretion of one of the end-products of adreno-cortical metabolism (the urinary 17-ketosteroids) was determined in a group of normotensive and hypertensive subjects.

Material and Methods. A review was made of microscopic sections of the adrenals of hypertensive and normotensive patients.* These specimens were prepared by members of the Department of Pathology in the course of routine postmortem examinations. In each instance, the entire cortex was studied grossly for adenomatous or hyperplastic changes. In addition, the width of the left ventricular wall was recorded and hypertrophy was regarded as present if the width exceeded 12 mm.[35] The total weight of the heart was taken to be increased if it exceeded the normals of each age group in the tables of Rössle and Roulet.[28] A search was also made for evidences of arteriolar sclerosis.

A patient was regarded as having had hypertension if two or more of the following criteria were present: (1) persistent systolic blood pressure of 140 mm. Hg or more, (2) persistent diastolic blood pressure of 90 mm. Hg or more, (3) width of the left ventricular wall exceeding 12 mm. (in the absence of rheumatic or luetic heart disease, and of hyperthyroidism), (4) increased total heart weight and (5) arteriolar sclerosis.

The clinical and necropsy records of 135 patients were thus reviewed. According to the criteria outlined above, 65 were classed as hypertensives and 70 as normotensives.

The second part of this study dealt with the excretion of 17-ketosteroids in normal subjects and hypertensive patients. As is generally known, the 17-ketosteroids are formed primarily from the secretions of the adrenal cortex, but they are also derived in the male from the testicular steroids. Since it is difficult to estimate accurately testicular activity in the male, this phase of the investigation was confined to female subjects in whom the entire 17-ketosteroid output may be considered as derived from the adrenal cortex.

The urinary 17-ketosteroids were determined† (with minor modifications) by the method of Friedgood and Berman[12] which is based on the reaction first described by Zimmerman.[37] The final calculations were made from a previously prepared curve using dehydroandrosterone‡ as standard material. In

* With the assistance of John J. Larkin, M.D., Department of Pathology, New York Post-Graduate Hospital.

† With the technical assistance of Julius Wiland, B.S., now Lieutenant, Sanitary Corps, Army of the United States.

‡ The dehydroandrosterone was supplied through the courtesy of Dr. Max Gilbert of the Schering Corporation.

our hands, this procedure gave excellent recoveries of known quantities of dehydroandrosterone added to urine.

Each patient was instructed in the manner of collection and refrigeration of the 24-hour urine specimen. Only one such specimen was collected from each patient, since the 17-ketosteroid excretion is reputed to be quite constant from day to day.[5,6,11]

For reasons already stated, these studies were confined to female patients; a total of 54 analyses were made. Forty were from hypertensive patients ranging in age from 28 to 70 years with an average systolic blood pressure of 200 mm. Hg (range 150 to 274) and an average diastolic blood pressure of 110 mm. Hg (range 80 to 148). Fourteen analyses were made from normotensive subjects with an age range of 20 to 76 years.

Results. Table 1 shows the incidence of hyperplastic or adenomatous changes in the adrenal cortex in 70 normotensive and 65 hypertensive patients as revealed by gross and microscopic necropsy material. No difference was found in the incidence of such changes in the two groups.

TABLE 1.—THE INCIDENCE OF HYPERPLASTIC OR ADENOMATOUS CHANGES IN THE ADRENAL CORTEX AND THE EXCRETION OF URINARY 17-KETOSTEROIDS IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

	Group	
	Normotensive	Hypertensive
Adrenal cortex:		
Hyperplastic or adenomatous changes:		
No. of subjects	33	30
%	47	46
Normal:		
No. of subjects	37	35
%	53	54
Urinary 17-ketosteroid excretion:*		
No. of subjects:		
Total	14	40
17-ketosteroid excretion, mg./24 hrs.:		
2.5–12.5	4	37
12.5–22.0	10	3
Average, mg./24 hrs.	14.2±4.0	8.4±4.3

* The significance of these findings was evaluated by the formula

$$t = \frac{\bar{\chi}_1 - \bar{\chi}_2}{\sqrt{\frac{N_1\sigma_1^2 + N_2\sigma_2^2}{N_1 + N_2 - 2}}} \cdot \sqrt{\frac{N_1N_2}{N_1 + N_2}}$$

for a small series and t was checked against Fisher's tables.[10] In this formula $\bar{\chi}_1$ represents the mean for the normals, $\bar{\chi}_2$ the mean for the hypertensives, N_1 the number of normal cases, N_2 the number of hypertensive cases, σ_1 the standard deviation of the normals and σ_2 the standard deviation of the hypertensives. t is 4.35 which represents a significant difference.

In 40 female patients with hypertension, the average daily output of 17-ketosteroids was less than in a control group of 14 normotensives. Four of 14 normal subjects excreted less than 12.5 mg. of 17-ketosteroids in 24 hours, whereas only 3 of the 40 hypertensives exceeded this figure. The significance of this finding was corroborated by a statistical analysis (see footnote, Table 1). In 3 hypertensives, the 17-ketosteroid excretion was relatively high (18.2, 18.7 and 22 mg. in 24 hours, respectively). It is interesting to conjecture that in these patients the hypertension may have had its origin in or at least may have been associated with hyperactivity of the adrenal cortex.

So-called "blood adreno-cortical substances (a-c bodies)" were also determined in the hypertensive and normotensive subjects;* but the results are not detailed here since the significance of such determinations is as yet not clearly defined. The method employed was that of Raab,[25] which is a modification of the Shaw[30]-Whitehorn[36] procedure. Apparently, the color reaction utilized in this method is not specific for adrenalin; ascorbic acid is one of several important interfering substances. These a-c bodies do not increase quantitatively in the blood when the blood pressure is elevated during the cold-pressor test in humans nor following the injection of renin in cats; there is, however, a close correlation between the rise in blood pressure and the concentration of a-c bodies in the blood of animals after the intravenous administration of adrenalin.[33] In the present study, the 14 normotensives showed an average of 9.65 ± 3.55 micrograms of a-c bodies in 100 cc. of blood, whereas the 40 hypertensives averaged 9.81 ± 3.13 micrograms. The difference between the two groups was statistically insignificant.

Discussion. The present findings confirm the observation of Dempsey[8] that nodular or adenomatous hyperplasia of the adrenal cortex is not regularly found in association with hypertension and that it occurs with considerable frequency in non-hypertensive cases. It appears safe to conclude, therefore, that hypertension is not necessarily accompanied by any specific alteration in the histology of the adrenal cortex. Likewise, it has been reported that the size of the adrenal gland is not altered by a preëxisting hypertensive state.[8,16]

Although the findings presented here indicate that the hypertensive tends to excrete less 17-ketosteroids in the urine than the normotensive, this cannot be taken as evidence of adreno-cortical hypoactivity. Browne and his co-workers[4] and, more recently, Horowitt and Dorfman,[15] have demonstrated the presence in urine of a substance with cortin-like properties which does not give the color reaction for 17-ketosteroids. Therefore, the evidence given here does not preclude the possibility of adreno-cortical hyperactivity in patients with hypertension. In fact, Selye[29] has produced hypertension and renal arteriolar sclerosis in rats by the administration of excessive doses of salt and desoxycorticosterone acetate. If, however, it can be demonstrated that the adrenal cortex of hypertensives does not produce an excess of cortin, the present studies on 17-ketosteroid excretion suggest a hypofunctioning adrenal cortex in patients with hypertension, reflecting perhaps a gland exhausted under the constant strain imposed upon it by the persistent elevation in blood pressure.

Conclusions. 1. There is no difference in the incidence of hyperplastic or adenomatous changes in the adrenal cortex of hypertensive and normotensive subjects.

2. The urinary excretion of 17-ketosteroids is significantly lower in hypertensive than in normotensive subjects.

3. Some theoretical considerations are offered to account for these findings.

* With the technical assistance of Samuel Member, B.S.

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FACTORS INFLUENCING FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS DUE TO SMALLPOX VACCINATION (VACCINIA)*

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Recent observations and studies have shown that smallpox vaccination (vaccinia) is capable of producing false positive serologic

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reactions for syphilis. Such reactions are of sufficient frequency and intensity to be a serious source of error in the serologic diagnosis of syphilis.

In 1940, Barnard[2] reported the case of a young man, recently vaccinated, who gave repeated strongly positive Kahn reactions. Mohr and associates[6] included a similar case in their report of the causes of biologic false positive reactions. Thomas and Garrity,[7] by statistical analysis of 20,000 recruits, concluded that smallpox vaccination followed by accelerated and non-immune reactions, was the probable cause for the increase in the incidence of false positive reactions for syphilis. One case was studied in detail.

It remained for Lynch *et al.*[5] to demonstrate conclusively, that smallpox vaccination was a frequent cause of false positive reactions. In a carefully controlled study on 263 persons with a primary vaccinia, they obtained an incidence of 16% positive individuals by one or more of the Kolmer, Kline, Hinton and Mazzini tests. The intensity of these reactions varied from ± to ++++. They appeared in 2 weeks and remained positive for 2 months in most instances. A few persisted for 4 months and one for 5 months. Apparently, individuals with accelerated and immune reactions were not included in the group.

An opportunity for a similar study was presented to us[3] recently. An importation of a case of smallpox near the Philadelphia area led to mass vaccination approximating one million persons. A group of individuals was chosen in whom a serologic test for syphilis had been performed within a reasonable time previous to the vaccination. There were 202 individuals ranging in age from 3 weeks to 84 years. Over one-half were between 20 and 30 years of age, consisting mostly of medical students and nurses.

Forty-four individuals developed a primary cutaneous (non-immune) reaction at the site of inoculation, 134 developed a local accelerated (vaccinoid) form and 24 were immune.

Out of 202 individuals on whom a single blood examination was performed, 19 were found to be positive by one or more of the Kolmer simplified complement-fixation test, the Kahn and Mazzini flocculation tests. They were examined from 10 to 57 days following vaccination, but 93.6% were done before the 43rd day. Twenty-five persons who gave a negative reaction 14 days after vaccination, were reëxamined 14 days later (1 month after vaccination). Four out of this group were now positive. No doubt additional positive individuals would have been detected if the entire group had been examined in a similar manner.

In all, 24 individuals out of 202 gave a false positive reaction for syphilis, giving an incidence of 11.8%. This figure included all individuals regardless of the type of vaccination reaction. Since the positive serologic reactions were about equally divided between the non-immune and accelerated groups and none occurred in the immune, the percentage of positive individuals would be higher, if the latter immune group were excluded.

The serologic reactions were mostly ++ or less in intensity (Table 1)

and would be classified as negative or doubtful. However, 22.4% were +++ or stronger. The positive individuals were reëxamined at regular intervals. At the end of 60 days, only 8 were still positive, while in 80 days, 4 were weakly positive. Two persisted for 100 days, and all became negative in 120 days.

TABLE 1.—NUMBER AND DEGREE OF INTENSITY OF SEROLOGIC REACTIONS ENCOUNTERED IN 202 INDIVIDUALS FOLLOWING SMALLPOX VACCINATION (FIRST STUDY)

Degree of reaction	±	+	++	+++	++++	Total
Kolmer	2	5	1	..	3	11
Kahn	5	6	3	1	3	18
Mazzini	6	9	8	6	..	29
Total	13	20	12	7	6	58

In order to show that the incidence of false positive reactions in this study was not due to chance alone, a survey was made of the number of positive individuals encountered in the same laboratory for 1000 tests of each type performed. When this figure was employed for calculating the significant difference, when compared to the experimental group of 11.8% in 202 individuals, the difference was found to be highly significant. Furthermore, the reactions persisted in the same individuals and gradually disappeared spontaneously. The smallpox vaccination was the only apparent factor operating.

Reports from other sources have added additional evidence to show that smallpox vaccination is an important cause of biologic false positive reactions for syphilis. Arthur and Hale,[1] in studying 95 soldiers, found that 14 (14.8%) gave a temporary false positive reaction. Their study was begun after the men had been recently vaccinated against typhoid fever, tetanus, smallpox and yellow fever. They concluded that the false reactions were the result of the combined inoculations of the routine Army immunizations.

Lubitz[4] reported an incidence of 13% positive serologic reactions to one or more tests in 100 individuals with a primary smallpox vaccination reaction. The pattern of the subsequent course of the tests was essentially the same as that followed in studies of Lynch and ours. Lubitz also showed that the positive serums did not give the heterophile antibody test, and storage of the serums for 2 to 17 days at 4° C. produced a marked reduction in the intensity of the serologic reactions when they were repeated. Syphilitic serum, on the other hand, dropped only slightly. Such a finding would imply that storage at low temperature might be used, in part, to differentiate the false from the true type of syphilitic reaction.

Analysis of the Second Study. In January, 1943, the entire student body of a medical school was vaccinated against smallpox. Subsequently, a new freshman class was enrolled, leaving three-fourths with a recent vaccination. Six months later the students were again subjected to vaccination, not only to smallpox, but to typhoid, paratyphoid fevers and tetanus. Since smallpox vaccination was given after the administration of typhoid vaccine and 2 injections of tetanus toxoid, an opportunity was offered to determine just what rôle such

immunization played in the production of false positive reactions for syphilis. It also offered additional data for the continued study of smallpox as a cause of false positive reactions. Other factors were also studied.

The second group for study was composed of men between the ages of 21 and 30 years. It included 323 individuals, three-fourths of whom were vaccinated for smallpox 6 months previously. Following a preliminary blood test they were revaccinated. Six individuals developed a primary cutaneous (non-immune) reaction, 71 developed an accelerated (vaccinoid) form, and 246 were immune. One month after the date of vaccination, a blood specimen was obtained and examined with the Kolmer, Kahn and Mazzini tests. No opportunity was offered for more frequent and prolonged observations. There were 15 individuals with 21 positive serologic reactions. Five of these occurred in the accelerated and 4 in the primary (non-immune) group, while 6 were immune. The serologic reactions in this study were mostly ++ or less in intensity. Twenty per cent were +++ or stronger, and occurred in the accelerated and primary (non-immune) types.

The large number of immune individuals in this second study contained 2.4% of weakly positive serologic reactions. The combined total for the accelerated and primary individuals amounted to 11.7%, which is almost identical with that of the first study (11.8%). The serologic tests taken before vaccination and used as control revealed an incidence of 1.6% positive individuals. These tests were done after typhoid and tetanus immunizations. Thirty days after vaccination, and including all individuals regardless of their vaccinia cutaneous reactions, 4.6% were positive. On this basis alone there is a significant difference in the increase which can be attributed to smallpox vaccination.

Summarizing the pooled data (Table 2) on 525 individuals, using a single blood test 30 days after vaccination, there were 270 immune cutaneous vaccinia reactions with 6 weakly positive individuals (2.2%). Out of 205 acclerated reactions 15 (7.3%) were positive, while 13 (26%) out of 50 primary (non-immune) were positive and included most of the strongly false positive tests for syphilis. Excluding the immune, 11% of the individuals with an accelerated or non-immune cutaneous vaccinia reaction were positive by one or more of the Kolmer, Kahn and Mazzini tests.

TABLE 2.—CUTANEOUS VACCINIA REACTIONS AND SEROLOGIC RESPONSE IN EACH TYPE, WITH A SINGLE SPECIMEN OF BLOOD AFTER 30 DAYS (COMBINED STUDY)

	Type of vaccinia reaction			
	Immune	Accelerated	Non-immune	Total
Number of individuals	270	205	50	525
Individuals with positive tests	6	15	13	34
Per cent	2.2	7.3	26	6.5

Per cent positive of accelerated and non-immune individuals, 11.

In view of Arthur and Hale's work[1] in which the false positive reactions were attributed to the combined effects of typhoid, tetanus,

smallpox and yellow fever immunizations, an attempt was made to clarify this problem. Smallpox vaccination alone is capable of producing false positive reactions for syphilis in 11 to 16% of individuals. No clear-cut evidence is available to show that other forms of immunization are capable of doing the same thing.

To verify experimentally if multiple immunizations, excluding smallpox, can produce similar false positive serologic reactions, the following investigation was undertaken. There were 314 men who had received a Kahn serologic test just prior to the first injection of typhoid (T.A.B.) vaccine and tetanus toxoid. Twelve days after the last of the 3 weekly inoculations of typhoid (T.A.B.) and 10 days after the second and 31 days after the first inoculation of tetanus toxoid, a sample of blood was obtained for serologic examination. Five individuals, giving an incidence of 1.6% had weakly positive serologic reactions. No test gave a stronger reaction than + in this group. In view of these findings, it cannot be said that typhoid and tetanus immunizations contribute materially to the problem of false positive reactions for syphilis.

The question arises whether non-specific stimulation with other antigens might cause a rise in the pseudo-syphilitic reagin of an individual who had been recently vaccinated and had developed a false positive serologic reaction. It was possible to assemble a group of 5 individuals who gave a false positive syphilitic reaction 6 months previously. They gave 8 positive reactions by one or more of the Kolmer, Kahn and Mazzini tests. In no instance were these individuals positive after immunization with typhoid vaccine and tetanus toxoid. A control group consisting of 17 men with similar vaccinia reactions and negative blood 6 months previously also failed to show any positive syphilitic reactions.

Since the majority of individuals had been vaccinated 6 months previously, what effect would revaccination have on the serology of those who gave false positive tests originally? Six individuals were available whose data were comparable (Table 3). All of the persons had returned to normal serologic tests 3 months previously and had a negative serologic reaction for all tests, before revaccination. Fourteen days following revaccination 1 gave a ++ Kolmer while another gave a ++ Mazzini. These returned to normal in 30 days, although 1 of the 2 showed a ± Mazzini at this time. The number of cases studied is not sufficient to draw conclusions, but can be used as a nucleus for further investigation.

TABLE 3.—SEROLOGIC RESPONSE FOLLOWING REVACCINATION OF PREVIOUSLY POSITIVE INDIVIDUALS

Case No.	Serologic tests 14 days after original vaccination			Serologic tests 6 months later			Serologic tests 14 days after revaccination			Type of cutaneous vaccinia reaction
	Kol.	Kahn	Maz.	Kol.	Kahn	Maz.	Kol.	Kahn	Maz.	
15	+	++	++	–	–	–	–	–	–	Immune
23	+	–	–	–	–	–	–	–	–	"
25	±	–	–	–	–	–	–	–	–	"
52	–	–	++	–	–	–	–	–	++	"
55	++	–	+	–	–	–	++	–	–	"
102	++++	++++	+++		–		–	–		"

It has been pointed out that the sera of individuals with false positive tests for syphilis have a rapid loss of the reagin which produces such

reactions. Lubitz, using the Kahn test, found that after standing in the ice-box at 4° C. for 2 to 17 days the titer of the serum fell appreciably, a ++++ reaction falling to ++, + or negative. The weaker positives fell proportionately. The titer of the serum from syphilitic patients remained the same or dropped slightly.

Five of our sera were retested after storage for 7 months in the ice-box at 4° C. Table 4 shows the result. The Kahn test showed an appreciable decrease in the weaker positives, but the Kolmer and Mazzini tests retained their sensitivity with only some decrease in the weakly positives. Our sera were not inactivated before storage.

TABLE 4.—SEROLOGIC TESTS ON POSITIVE UNALTERED SERUM AFTER STORAGE AT 4° C. FOR 7 MONTHS

	Original tests (2-5-43)			Tests 7 months later (9-7-43)		
Case No.	Kol.	Kahn	Maz.	Kol.	Kahn	Maz.
9 . . .	+	−	++	++	−	±
15 . . .	−	+++	+++	±	+	++
32 . . .	−	++	++	−	±	±
55 . . .	++	−	+	+	−	+
102 . . .	++++	++++	+++	++++	+++	++++

Comment. The total of both groups so far studied is 525 individuals, the majority of whom were male adults between 20 and 30 years of age. To draw accurate conclusions as to the incidence of biologic false positive tests for syphilis due to smallpox vaccination, several factors must be taken into consideration, one being the type of vaccination reaction. Lynch *et al.* basing their study on primary reactions, found 16% positive individuals with the use of multiple serologic tests, while Lubitz, who apparently employed only one serologic test, found 13% positives in primary reactions and none in accelerated and immune. In the 26 cases of Thomas and Garrity, who also employed the Kahn test only, 3 were immune, while the other 23 were about equally divided between the non-immune and accelerated. Twenty-four immune individuals in our first study were all negative.

In our second study, however, 6 out of 246 immune individuals (2.4%) gave weakly false positive serologic reactions. There are several possibilities for this finding. First of all, smallpox vaccination with an immune cutaneous response may be capable of producing such reactions. Secondly, this low incidence may be representative of the general population of the same age group by the techniques employed. Thirdly, recent revaccination may produce a detectable increase in the reagin of a previously positive individual. Such suggestive evidence has been presented in this study in a very small number of individuals, too small to draw conclusions.

From a practical clinical standpoint, it is extremely important to correlate the incidence of false positive tests of the blood with each type of vaccinia cutaneous reactions. A person with a positive syphilitic blood test who has been vaccinated recently, is quite likely to remember, on questioning, as to whether or not a scab was formed. If there is no history of a scab, the reaction may be considered as immune

and the serologic test interpreted accordingly. If, however, a scab was formed, denoting an accelerated or non-immune (primary) reaction, vaccination should be suspected as a probable cause of the positive syphilitic serologic test. The presence or absence of a vaccination scar cannot be relied upon entirely as evidence of the type of skin reaction, since many accelerated reactions may leave little or no marking within the period of the presence of a false positive test for syphilis.

The decrease in the intensity of the serologic reactions on storage at 4° C. as observed by Lubitz in the interpretation of the tests may be of some value. Since such a decrease occurs appreciably with one serologic test and only slightly with others, the value of this observation is minimized.

The transitory nature of false positive reactions is the most important characteristic in the differential interpretation so far. The vast majority disappears in 60 days. Very few persist for a longer period, and then only as a weak reaction of+or less. This has been the experience of other investigators already cited.

In view of Arthur and Hale's report, it was desirable to analyze the probable causes of such false reactions which follow routine Army immunizations. Typhoid (T.A.B.) and tetanus immunizations were not found to contribute materially to the incidence of false positive reactions for syphilis. Thomas and Garrity found that typhoid inoculations had no bearing on the false positive Kahn diagnostic test. Observations on a limited number of cases also demonstrated that immunization with these antigens did not reactivate a false positive test in individuals who gave such tests from accelerated and non-immune vaccinia vaccinations 6 months previously.

The ability of smallpox revaccination within 6 months to reactivate a false positive reaction for syphilis requires additional investigation. Two individuals, out of 6 studied, again gave false positive tests which disappeared in 30 days. The cutaneous vaccinia reactions in all 6 were of the immune type. The blood serology prior to revaccination had returned to normal. Obviously, this phase of the problem is extremely important, and requires much additional data to prove conclusively if findings in such a small series are due to chance or to actualities.

Summary. 1. Smallpox (vaccinia) vaccination followed by an accelerated or primary (non-immune) cutaneous response is a newly recognized and important cause of biologic false positive serologic reactions for syphilis. The incidence of such reactions is at least 11 to 16%.

2. The available evidence justifies the conclusion that an immune response to smallpox vaccination can be disregarded as a significant cause of a false positive serologic reaction for syphilis.

3. The false positive serologic reactions for syphilis are transitory. They appear within 2 weeks of the date of vaccination and disappear, in most instances, within 2 months. A few persist as extremely weak reactions as long as 4 months.

4. Typhoid (T.A.B.) and tetanus toxoid immunizations have no

significant bearing on the production of false positive serologic reactions for syphilis.

5. Suggestive findings are presented to show: (*a*) that recently vaccinated individuals who gave a positive serologic reaction, do not have a reactivation of their positive reactions following typhoid and tetanus immunizations 5 months later, and (*b*) individuals with a false positive serologic reaction, when revaccinated for smallpox within 7 months, may again present a weak serologic false positive response for syphilis, even though the second vaccinia reaction is of the immune type.

6. Positive serums stored in the ice-box at 4° C. for 7 months have a variable loss of titer. Such loss is not sufficient to be of differential diagnostic value.

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PHOSPHORUS POISONING

A Report of 16 Cases With Repeated Liver Biopsies in a Recovered Case

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Poisoning due to phosphorus is regarded as uncommon in the United States. Reports of only 9 fatalities could be found in our medical journals in the past 2 decades,[4,5,6,9,10,15,20,27,30,31] but in 1927 the American Museum of Safety listed the deaths of 16 children who ate fireworks.[7,24] These reports, together with the 4 fatalities reported here, suggest that the incidence of phosphorus poisoning may be greater than that indicated by a careful perusal of our medical literature.

The relative infrequency of phosphorus poisoning in the United States is probably due to the prohibition of the manufacture and sale of matches made from yellow phosphorus. In China[13] and Japan,[22] where the sale of this type of match is permitted, the number of cases of phosphorus poisoning has increased in recent years. One milligram of yellow phosphorus per kilo of body weight is usually fatal, while red phosphorus is relatively nontoxic even in large amounts.[8]

Yellow phosphorus-containing roach poisons and fireworks are still available in the United States and represent an obvious danger to children. Five of the 9 fatalities reported in the American literature resulted from the ingestion of small amounts of fireworks by children.[5,6,10,20,27] The other 4 fatalities were due to the taking of roach poison.[4,9,15,30,31] Roach poison containing about 2% yellow phosphorus is widely sold at most drug and grocery stores.

At Charity Hospital in New Orleans, 16 patients, 4 of whom died, have been treated for phosphorus poisoning since 1920. This represents an incidence of 1 in every 57,700 admissions. The purpose of this paper is to report the clinical picture of phosphorus poisoning in these patients and to discuss in detail the case of 1 surviving patient in whom morphologic liver damage is apparently progressing to portal cirrhosis..

Case Reports. *Fatalities.* Case 1. C.C., a 9 month old negro male child, ate a piece of potato covered with a layer of roach poison and died 10 hours later. There were no gastro-intestinal symptoms, but the child was semicomatose when seen at the hospital 4 hours after having ingested the poison. His temperature was 101.2° F. and his pulse rate 145 per minute, with respirations 45 per minute. Gastric lavage was done at once and 100 cc. of 5% glucose with 100 cc. of normal saline were given, but the infant died 6 hours after admission. The diagnosis made by the coroner at autopsy was phosphorus poisoning.

Case 2. M.G., a 65 year old housewife, swallowed one teaspoonful of roach poison and died 52 hours later. She was admitted to the hospital 12 hours after having taken the phosphorus-containing poison and gastric lavage was immediately performed. Throughout the day she complained of epigastric pain and progressive weakness. She was semistuporous, weak and in shock, with a blood pressure of 60/40 mm. Hg and a pulse rate of 120 per minute. The low blood pressure continued despite a blood transfusion of 500 cc. and the intravenous administration of 100 cc. of gum acacia in 400 cc. of saline. The patient received 1200 cc. of fluid and excreted 600 cc. of urine. On the day of death the blood urea nitrogen was 46 mg. per 100 cc.; creatine was 5.3 mg. per 100 cc. and the blood sugar was 139 mg. per 100 cc. There was a trace of albumin in the urine and 2 to 3 red blood cells and 4 to 6 white blood cells were seen per high-power field. The coroner's diagnosis was phosphorus poisoning.

Case 3. Y.R., a 20 year old white housewife, was brought to the hospital in a state of coma and died on the same day that she had taken an undetermined amount of roach poison. The coroner's diagnosis was phosphorus poisoning.

Case 4. J.R., a 15 month old infant, was admitted with a history of 5 days' abdominal pain and intermittent vomiting which had not been severe enough to keep her from play. On the evening of the 4th day she became comatose. She was in deep coma when admitted to the hospital on the 5th day and vomited coffee ground material shortly afterwards. She was jaundiced and stuporous and on one occasion drew her head and neck back so that she appeared opisthotonic. No true convulsions were seen. The family was unable to say whether the child had taken poison of any kind but admitted that roach paste had been "set out." A spinal tap was done and clear fluid under normal pressure was obtained. The child died just as the needle was withdrawn.

Spinal fluid examination and urinalysis were normal. The blood sugar was 99 mg. per 100 cc., the blood glucose 27 mg. per 100 cc. and the carbon dioxide combining power 30 volumes per cent. The icterus index was 50.

At necropsy the heart weighed 40 gm. and appeared to be slightly dilated. The myocardium was pale. Slight atelectasis of the posterior portion of both lungs was noted. The liver weighed 500 gm. (normal weight at 15 months, 330 gm.), was 5 cm. below the costal margin, bright yellow in color, and a loss

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of lobular arrangement was seen on cut section. No gross abnormalities of the pancreas, kidneys, adrenals or spleen were noted. The brain weighed 700 gm.; its gyri were flattened and its sulci narrowed.

Significant microscopic abnormalities were seen in the liver, kidney and brain. In the liver, there was extensive fatty metamorphosis with vacuolization of almost all the liver cells about the portal areas. The rest of the liver cells were swollen and granular. Moderate polymorphonuclear leukocytic and lymphocytic infiltration was seen in some of the portal spaces, but there was no connective tissue proliferation. In the kidney the cells of the tubules were granular and swollen, narrowing the lumen of the tubules markedly and closing it entirely in some portions. Each renal epithelial cell showed numerous very small vacuoles. The glomeruli were normal. The brain showed moderate congestion of the vessels in the leptomeninges and in the brain substance. There was no evidence of inflammatory cell infiltration in either of these locations. An occasional vessel showed a collar of recent hemorrhage in the perivascular space. Vacuolization of the brain matrix and "lacunization" of the nerve cells indicated cerebral edema.

Recoveries. Case 5. M.B., a 30 year old housewife, took 1 ounce of roach paste containing phosphorus with suicidal intent. Twenty minutes later she developed epigastric fullness, became nauseated and vomited. She vomited frequently for 4 or 5 hours and then developed a profuse watery diarrhea which was accompanied by abdominal cramps that kept her awake all night. She continued to vomit everything taken by mouth, but the diarrhea subsided after 6 hours. She was admitted to the hospital 18 hours after having taken the poison. Her stomach was pumped out immediately and she was given 1000 cc. of 10% glucose intravenously. She was emaciated, complained of abdominal pain and the upper abdomen was moderately tender to deep palpation. The blood pressure was 100/80 mm. Hg, the pulse 105 per minute and the temperature 101° F. The blood and spinal Wassermann tests were strongly positive and a 1-plus sugar and a trace of albumin were found in the urine. Symptoms cleared rapidly and except for a slight temperature for 3 days the patient had no complaints. No jaundice was seen.

Case 6. E.M., a 30 year old white female, took an undetermined amount of roach paste containing phosphorus on a slice of bread. Almost at once she developed violent cramping abdominal pains. Gastric lavage was done 3 hours after the poison had been taken and 4 ounces of mineral oil with 2 ounces of 50% magnesium sulfate were left in the stomach. The blood pressure was 100/70 mm. Hg, the abdomen moderately tender to deep palpation and the liver could just be felt. No jaundice was noted. Routine urinalysis and blood studies showed no abnormalities. The patient was given 3 infusions of 1000 cc. of 5% glucose in the first 24 hours. During this time she complained of abdominal cramps and passed 8 watery stools. She had a few cramping pains during the next 3 days, but was otherwise well at the time of discharge on the 5th day.

Case 7. E.W., a 35 year old male, took rat poison containing 2.5% phosphorus with suicidal intent. He was admitted to the hospital 12 hours later in a state of coma. Gastric lavage was done immediately and a solution of 2.5% magnesium sulfate was left in the stomach. An intravenous infusion of 3000 cc. of 10% glucose was administered. The patient was restless and vomited frequently. A few superficial ulcers were noted on the reddened mucous membrane of his mouth and tongue. There was slight epigastric tenderness. On the 2nd day the symptoms had disappeared and he was discharged on the 5th day. Jaundice was not seen.

Case 8. G.M., a 23 year old housewife, took 2 teaspoonsful of roach paste in an attempt at suicide. Her physician was called at once and he administered 11 glasses of salt water which caused the patient to vomit profusely. Then a dilute mixture of copper sulfate, potassium permanganate and turpentine was left in the stomach. Six hours later the patient was admitted to the hospital in no acute distress but with a blood pressure of 98/54 mm. Hg.

She vomited 11 times on the 1st day, 8 times on the 2nd and complained of

mild abdominal cramps and generalized body aches. She was given 1000 cc. of 5% glucose on the 3rd day and had no complaints. Jaundice was not seen and she was discharged on the 7th day.

The admission laboratory findings were 3-plus albuminuria, occasional granular casts in the urine with blood levels of 52.5 mg. of non-protein nitrogen per 100 cc., 25 mg. of urea per 100 cc. and 105 mg. of sugar per 100 cc. On the 3rd and 7th days the urine was negative and the blood urea had fallen to 15 mg. per 100 cc. of blood on the 7th hospital day.

CASE 9. F.C., a 39 year old white housewife, took an undetermined quantity of roach poison with suicidal intent. She was admitted to the hospital on the same day and was semistuporous and restless. Immediate gastric lavage was done and the patient vomited clear, phosphorescent fluid 3 times. She was completely well on the following day and left the hospital.

CASES 10 to 15. Six other patients who took undetermined amounts of roach poison recovered quickly. The patients were 2 white males, aged 25 and 42; 1 white female aged 51; 2 infant girls aged 18 months and 1 year; and a 3½ year old boy. All had a gastric lavage within 2 hours after taking the poison and exhibited no symptoms except mild nausea. All were discharged from the hospital within 10 to 20 hours after admission.

CASE 16. G.A., a 61 year old unemployed white male, swallowed an ounce of roach paste containing 2% phosphorus at 12:30 A.M. on April 2, 1942. Within 30 minutes he began to vomit, but between paroxysms he managed to consume another ounce of roach paste. The vomiting became increasingly severe and he developed cramping abdominal pains and began to pass frequent stools which were first solid and then watery and later contained dark red masses "like Concord grapes." The vomitus and stools were put in the same container and emitted a greenish blue light. Vomiting subsided but the diarrhea and abdominal pain persisted throughout the first 48 hours. On the morning of April 4 the patient's landlady found him in a semistuporous state with several self-inflicted lacerations on his left wrist.

He was admitted to the hospital at 4:25 P.M. on April 4, 64 hours after having taken the poison, semicomatose and deeply jaundiced. The blood pressure was 92/62 mm. Hg, the pulse 120 per minute and the temperature 96° F. The liver was felt 6 cm. below the costal margin in the mid-clavicular line. Superficial cuts were noted on the left wrist and many shallow ulcers were seen on the mucous membrane of the mouth, tongue and oral pharynx.

Gastric lavage was done immediately and 100 cc. of mineral oil were left in the stomach. The patient was then given 2000 cc. of 10% glucose intravenously and this was repeated at least once daily for the first 10 days. An eggnog mixture containing 60 gm. of protein, 300 gm. of carbohydrate and 30 gm. of fat was administered each day by duodenal intubation. Vitamin concentrates and 2 oz. of mineral oil were also given. After 10 days the patient was able to eat and was placed on a diet containing 450 gm. of carbohydrate, 120 gm. of protein and 70 gm. of fat.

Throughout the 1st week the patient was semistuporous. He vomited occasionally and passed 15 to 20 loose involuntary stools daily during the 1st week and 4 to 5 stools daily for the next 5 days. These were clay colored from the 5th to the 9th hospital days. Three blood transfusions were given during the 1st week. He was markedly jaundiced during this period and the liver was felt 6 to 8 cm. below the costal margin. After the 19th day of illness, improvement was quite rapid and 30 days after the ingestion of the poison the jaundice had markedly diminished and the liver was just palpable. Early in the 7th week there was a 1-plus pitting edema of the ankles, but this disappeared with continued rest in bed. The patient was discharged well on May 28, 1942, the 54th hospital day. He was readmitted for study on July 1, 1942, feeling "perfectly well." At this time all laboratory tests gave results within normal limits. The liver was barely palpable and the spleen could not be felt.

Pertinent laboratory findings are given in Tables 1 and 2. The hemoglobin varied between 10 and 12 gm. per 100 cc., the red blood cell count between 3.2 and 5.4 millions per c.mm. Studies of the morphology of the blood and

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bone marrow cells showed only a mild toxic reaction. During the 2nd week of hospitalization the white blood count varied between 11,000 and 16,000, but later it was within normal limits. The levels of the blood calcium and phosphorus were not abnormal and the prothrombin time was normal on April 11 and 21. On May 1, the intravenous bromsulfthalein test showed 50% retention in 5 minutes and 30% in 1 hour. On May 13 there was no retention at the end of 30 minutes. The hippuric acid test was normal on May 17 and July 1.

TABLE 1.—CASE 16, SHOWING THE FINDINGS IN THE URINE AND STOOLS AND INDICATING THAT THERE WAS COMPLETE BILIARY OBSTRUCTION FROM APRIL 10 TO 15, 1942

Urinalyses				Stool analyses		
Date (1942)	Bilirubin	Urobilinogen	Microscopic	Date (1942)	Color	Stercobilinogen
4- 5 (3rd day)	Tr.	+1:10	Few crystals, no WBC or RBC	4- 6	Black	1+
4- 8	4+	−1:10	Many WBC, few hyaline and gran. casts	4- 8	Brown, watery	1+
4-10	4+	None	Bile-stained casts	4- 9	White	Tr.
4-12	4+	None	Tyrosine crystals 4+, gran. and hyaline casts	4-10	Soft, chalky white	0
4-14	4+	None	Same	4-12	Same	0
4-15	4+	Faintly positive	10 WBC per hpf, occ. gran. cast (bile stain+)	4-13	Same	Tr.
4-16	3+	+1:10	20 WBC, occ. gran. cast (coarse)	4-14	Pale yellow	1+
4-17	3+	+1:40	5 WBC per hpf	4-17	Liquid yellow	1+
4-19	+	+1:640	Occ. WBC	4-18	Golden yellow	4+(1:160)
4-21	+	+1:320	10 WBC per hpf	4-23	Yellow	+1:320
4-22	+	+1:160	Few epith. cells, no WBC per hpf	4-29	...	+1:80
4-23	±	+1:80	12 WBC per hpf			
4-25	0	+1:10	—			
4-29	0	+1:10	—	7- 6	Yellow	Strongly +
7- 6	0	+1:10	Neg.			
9-14	0	+conc.	Neg.			

The patient was readmitted September 24, 1942, complaining that pus had been draining from his right ear for 2 days. The scleræ were slightly yellow and the right ear drum was injected and perforated. The liver was barely palpable on deep inspiration, but the spleen could be felt for the first time. The icteric index was 15.6 and the blood bilirubin too low to read. The intravenous hippuric acid test showed slight impairment of liver function (Table 2). He was discharged apparently well on the 5th hospital day and was advised to continue to take the high-protein, high-carbohydrate diet previously prescribed.

Liver Biopsy Studies of Patient No. 16. *First Biopsy* (33rd day of illness). The specimen consisted of a cylindrical piece of liver tissue which measured about 1 cm. in length and 0.1 cm. in diameter. No gross changes were noted. Microscopic serial sections were made. The general architecture was preserved. The cytoplasms of the liver cells had a foamy appearance and showed a moderate degree of vacuolization. An occasional area of focal necrosis (Fig. 1) was noted which consisted of several necrotic liver cells infiltrated by a few polymorphonuclear leukocytes. The largest of these areas measured about 60 microns through the greatest diameter. Finely granular, yellowish brown pigment was present within the cytoplasm of the Kupffer cells and of the liver cells. The pigment was rather uniformly distributed throughout the liver lobules. The periportal connective tissue was somewhat increased in quantity (Fig. 2) and was infiltrated with a moderate number of polymorphonuclear leukocytes. The bile ducts were not necrotic and contained no inspissated bile. Special stains revealed that some of the pigment within the liver cells contained iron, and hence was hemosiderin. The majority of the pigment granules, however, was neither hemosiderin nor hemofuscin.

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TABLE 2.—CASE 16, SHOWING THE BLOOD CHEMICAL FINDINGS, WITH FIRST AN INCREASE AND THEN A DECREASE IN THE ICTERUS INDEX; THE LIVER FUNCTION TEST; AND BLOOD AND MISCELLANEOUS STUDIES

	Blood chemistry*.								Liver function tests				Blood count*		
Date (1942)	Urea	Glucose	CO_2	Chlorides	P	Bilirubin	Icterus index	Total serum proteins	Bromsulphthalein	Cephalin flocculation	Hippuric acid*	Prothrombin time	Hgb.	RBC (in millions)	WBC
4- 6	51.6	133	..	..	..	17.5	125.0	..	...	..	..	..	12.0	4.0	6,720
4-10	..	..	..	..	3.3	..	125.0	..	...	+++					
4-11	20.0	..	37	..	3.6	21.8	166.0	..	...	..	..	..	..	4.5	14,000
4-13	20.0	..	..	562	3.3	..	..	4.07							
4-16	..	..	54	562	..	8.8	143.0	..	...	..	..	..	13.2	3.41	18,050
4-20	15.7	87	..	..	..	..	..	4.77							
4-21	..	..	..	..	..	..	..	..	...	..	..	Normal			
4-23	..	..	..	..	..	7.4	50.0								
4-29	..	..	..	..	..	..	35.0	..	...	+	..	..	12.0	3.94	8,320
5- 4	..	..	..	..	..	..	..	..	30%—1 hr.						
5-13	..	..	..	..	..	..	..	..	0%—1 hr.						
5-18	22.8	..	..	..	..	..	..	5.11	...	Neg.					
5-19	..	..	..	..	..	..	..	..	...	..	0.54 mg.	..	11.5	3.6	5,250
6-26	15.1	114	48	..	cholesterol 166		..	6.51	...	Neg.	0.82 mg.				
7- 6	..	..	..	..	too low to read		9.2								
9-24	..	..	..	..	"	"	15.6	6.51	...	..	0.73 mg.	..	13.0	4.6	4,700

Miscellaneous Blood Studies (*Bone Marrow and Blood Morphology*. 4–17–42: WBC show marked shift to left with toxic granules. Bone marrow appear sslightly hyperplastic and shows a granulocytic, myelocytic stimulation. Bleeding and clotting times normal on 4–5–42. K & K negative (unsatisfactory). Sed. rate 18 mm. per hr. on 4–13–42. 4–21–42: Kline and Kolmer strongly +. Spinal fluid K & K negative. 4–29–42: K & K strongly +.

* Intravenous hippuric acid test.

Second Biopsy (45th day of illness). The specimen consisted of a cylindrical piece of liver tissue which measured about 1 cm. in length and about 0.1 cm. in diameter. No gross changes were noted. Microscopic serial sections were made. The general architecture was preserved. No areas of focal necrosis were present but some of the liver cells showed vacuolization of their cytoplasms. The quantity of periportal tissue was increased over that which was seen in the first biopsy. It showed finger-like extensions of fibrosis entering the liver parenchyma for distances equaling the diameter of 6 to 8 liver cells (Fig. 3). A moderate number of polymorphonuclear leukocytes as well as lymphocytes infiltrated the connective tissue. The type distribution of pigment was similar to that seen in the first biopsy.

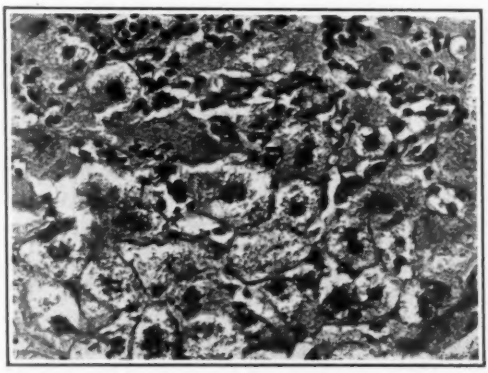

FIG. 1.—Photomicrograph of center of liver lobule showing small area of focal necrosis. Biopsy 33 days after onset of illness. H. and E stain. (× 276.)

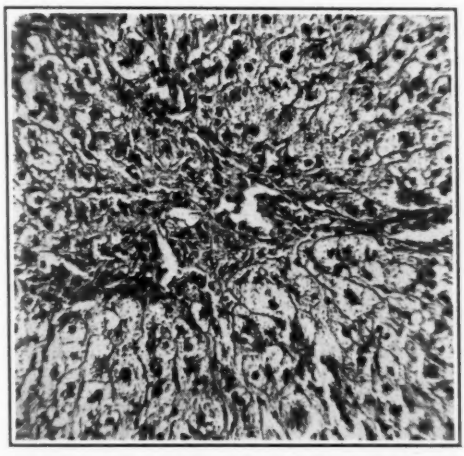

FIG. 2.—Photomicrograph of portal canal showing inflammatory cell infiltration into the supporting connective tissue. Biopsy 33 days after onset of illness. H. and E stain. (× 276.)

Third Biopsy (86th day of illness). The specimen consisted of a cylindrical piece of tissue which measured about 0.3 cm. in length and 0.1 cm. in diameter. No gross changes were noted. Microscopic serial sections were made. The general architecture was somewhat distorted because of the periportal fibrosis.

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Only a few vacuoles were noted in the cytoplasm of the liver cells and no foci of necrosis were present. The quantity of the periportal connective tissue was greater than that noted in the previous biopsy. The connective tissue extended further out into the liver parenchyma and in some places the connective tissue of two portal spaces joined each other (Fig. 4). A moderate number of inflammatory cells, the majority of which were lymphocytes, were present in the periportal connective tissue. A few polymorphonuclear leukocytes were also present. There was no change in the type and distribution of the pigment.

FIG. 3.—Photomicrograph of portal canal showing finger-like extensions of fibrosis entering the liver parenchyma. Biopsy 45 days after onset of illness. H. and E. stain. (× 144.)

FIG. 4.—Photomicrograph showing the fusion of fibrotic extensions of adjacent portal canals. Biopsy 86 days after onset of illness. H. and E stain. (× 86.)

Fourth Biopsy (191st day of illness). The tissue measured about 1.5 mm. in length and 0.5 mm in width. Microscopic serial sections were made. Two portal canals were present in this fragment of tissue. The liver cells were fairly well preserved and showed only a few very small vacuoles in their cytoplasms. The quantity of periportal connective tissue was similar to that which was observed in the last biopsy but the collagen content was greater.

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Comment. The diagnosis of phosphorus poisoning rests upon a history of the ingestion of phosphorus, the recovery of phosphorus from the vomitus or stools and the presence of toxic symptoms. In most instances, the history of ingestion of phosphorus, the characteristic odor and phosphorescence of the vomitus or stools, the occurrence of severe abdominal pain, emesis, icterus, ecchymosis, coma or convulsions, permit easy diagnosis. In the absence of a history, accurate diagnosis is difficult.

According to Thayer and Wolf,[29] symptoms appear soon after the ingestion of the poison in only 10 to 15% of the cases. Hours and even days may elapse in the majority of instances before symptoms of poisoning occur. Abdominal pain, nausea, emesis, thirst, jaundice, diarrhea, ecchymosis, coma, delirium and convulsions are, in the order named, the most frequently encountered symptoms. Abdominal tenderness, enlargement of the liver and stupor or coma are the usual physical findings. Laboratory studies may reveal uremia, anemia and evidence of liver damage.

In our patients, symptoms were noted soon after the ingestion of the poison in 4 cases and late in 4 cases. The remaining patients had seen a physician soon after taking the poison. Abdominal pain, nausea, emesis, weakness, diarrhea and coma were the most frequently noted symptoms. Jaundice was seen only twice. Generalized abdominal tenderness was noted in 8 cases and enlargement of the liver in 2.

Six of our patients admitted having taken the poison with suicidal intent; 4 took it accidentally. In Europe, many suicides due to the ingestion of phosphorus have been reported,[3,11,19,23,28] but only 1 of the 9 fatalities reported in our literature was listed as suicide.

Ten to 15% of patients taking yellow phosphorus die within 24 hours and 85% within 7 days.[29] Early death is apparently due to shock resulting from the general toxic effect of the poison on body cells. The same clinical picture preceding death is often observed in patients who take mercury.[17] Patients 1 and 2 were admitted to the hospital in a state of shock and coma and died 10 and 12 hours respectively after taking roach paste. Patient 3, who survived 52 hours after taking roach paste presented an identical picture. None of these 3 patients showed characteristic postmortem changes.

Fatal cases that survive more than 3 to 4 days usually show definite evidence of liver damage (jaundice, urobilinogenuria, bilirubinuria and coma). Fatty metamorphosis of the liver and tubular damage in the kidneys are the usual morphologic findings. Patient 4 was jaundiced and comatose and at necropsy showed fatty metamorphosis of the liver, tubular damage to the kidneys, and evidence of cerebral edema.

Patient 16 had complete obstruction of the outflow of bile from the liver for 4 days, evidenced by the total absence of bile pigments in the stool and of urobilinogen in the urine (Table 1). With the reappearance of bile pigments in the stools and urobilinogen in the urine, the liver became smaller. This temporary complete obstruction to the outflow of bile was probably due to swelling of the liver parenchyma as well as the periportal inflammatory reaction. The persistence of the jaundice

was probably due to impairment of liver cell function. This patient has been followed in the clinic for 9 months and feels perfectly well. Moreover all the tests of liver function are within normal limits. His liver, once palpable 8 cm. below the costal margin, can no longer be felt and spider angiomas have not been seen. However, after 9 months his spleen has become palpable.

Twelve of our patients recovered, 6 without any symptoms except mild nausea and discomfort. Six complained of nausea, moderately severe emesis and abdominal cramps. All vomited spontaneously 20 to 60 minutes after taking the poison and later had a gastric lavage. It is not difficult to know definitely why these 12 patients survived and the other 4 died, since all 12 of these patients vomited promptly after taking the poison or had the poison washed from the stomach within 2 hours. This appears to us to be the deciding reason for their survival. The 4 patients who died failed to vomit until 10 hours after the poison had been taken. Our histories are not accurate enough to detect any differences in the amount of poison taken.

Treatment demands immediate removal of the poison from the stomach, as well as measures to prevent absorption of phosphorus. Oxidation of the phosphorus with potassium permanganate, hydrogen peroxide, oil of turpentine and copper sulfate have been tried but not established as effective.[26] Atkinson[2] has shown that the administration of mineral oil to dogs a few minutes before or after feeding phosphorus will save the animals. Phosphorus is soluble in the mineral oil which is not absorbed from the gut, so it would seem advisable to leave 100 to 200 cc. of mineral oil in the stomach after lavage. Potassium permanganate (1:5000 sol.) can be left in the stomach to convert yellow phosphorus to harmless phosphates.

Once absorption has taken place, the treatment must be directed as far as possible to sparing the organs most severely damaged by phosphorus, that is, the liver and kidneys. It has been demonstrated that a high-protein, high-carbohydrate and low-fat diet will protect animals from toxic liver injury.[12,16,18,21,25,32] A diet such as that given Case 13 (450 c., 120 P., 70 F.) should be administered each day, supplemented by a high intake of vitamin B complex, with a fluid intake of at least 3000 cc.

Patient 16 is of special interest because we were able to follow by means of repeated liver biopsies the morphologic changes ensuing over a $6\frac{1}{2}$ months' period after the ingestion of phosphorus. Based upon the serial biopsies obtained from this patient, the findings in the human liver as a result of severe phosphorus poisoning with recovery, consisted of parenchymatous degeneration and fatty metamorphosis of the liver cells in the early stages. This is associated with small areas of focal necrosis of the liver cells and an acute inflammation of the periportal connective tissue. Within 45 days there was no evidence of focal necrosis and there was a decrease in the cytoplasmic degenerative changes. Meanwhile, there was an increase in the inflammatory cell infiltration and lymphocytes replaced the polymorphonuclear leukocytes as the predominant cell.

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A progressive increase in the periportal connective tissue occurred. On the 33rd day there was only a slight increase, but on the 86th day the connective tissue extensions from two adjacent spaces had joined each other and produced a "pig" liver lobule. The quantity of tissue obtained at the last liver biopsy, 191 days after the onset of illness, was too small to determine whether this periportal fibrosis was still progressive or whether some regression had occurred.

The lesions seen in the liver biopsy specimens taken from this patient closely resemble those produced by feeding phosphorus to dogs.[1,14] Cirrhosis appeared in the livers of dogs after a similar interval of time. Further biopsy examinations and studies of this patient will be made at 6 month intervals.

Summary. 1. In the United States most of the deaths due to phosphorus poisoning result from the ingestion of roach paste or fireworks.

2. Patients may die in a shock-like state within 24 hours after the ingestion of yellow phosphorus.

3. Prompt removal of the poison by emesis or lavage is essential to the recovery of patients who have taken a fatal dose of phosphorus.

4. A diet high in protein and carbohydrate and low in fat should be given to protect the liver and the daily fluid intake should be maintained between 3000 and 4000 cc.

5. The anatomic changes in the human liver in acute phosphorus poisoning with recovery showed focal necrosis, fatty metamorphosis and parenchymatous degeneration with acute inflammation of the portal canals in the early phase of illness. The late phase was characterized by periportal connective tissue proliferation histologically compatible with early portal cirrhosis.

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ACUTE MENINGOCOCCAL ENCEPHALOMYELITIS

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IT is now recognized that although invasion of the body by meningococci usually results in meningitis, this is not inevitable and other organs may be affected either concomitantly or independently. For example, purpura and cutaneous eruption are so common that the disease has been called spotted fever. The organism most frequently associated with the so-called Waterhouse-Friderichsen syndrome, in which there is massive adrenal hemorrhage, is the meningococcus. Acute meningococcal endocarditis has been occasionally observed. Chronic meningococcal septicemia is a distinct entity and is not infrequent. Meningococcal encephalomyelitis is one of the less common forms of infection; it is given only brief consideration in even the larger textbooks, and only few cases are recorded in the literature. Careful microscopic studies of autopsy material of cases of meningococcal meningitis might not improbably disclose involvement of substances of brain and cord not suspected upon gross examination.

The largest series of cases of meningococcal meningoencephalitis so far reported is that of Banks and McCartney. In a study of 10 cases observed in an epidemic of meningococcal meningitis in England during the winter of 1941–1942, they found several with encephalitis and myelitis. Their analysis of the clinical data showed that in most instances, the involvement of brain and cord can be diagnosed during life.

The following case is reported because (*a*) there was several unusual features, and (*b*) it seems well to add to the literature of this disease, so that ultimately a complete description of the disorder can be provided.

Case History. A.W.S., a white male, 27 years old, was admitted to hospital on April 27, 1943, complaining of headache, backache and fever which had been steadily increasing for 24 hours. Just before admission the patient became nauseated and vomited. The past medical history and family history were negative except for one attack of malaria in the autumn of 1942.

On admission, the temperature was 101° F.; pulse, 116; respirations, 15. The patient was acutely ill, vomiting and feverish. The pupils were small,

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reacted normally to light and in accommodation, the reflexes normal. There was questionable stiffness of the neck, which at the time was attributed to the severe headache. The naso-pharynx, chest and abdomen revealed no abnormal signs.

A tentative diagnosis of influenza and possible benign tertian malaria was made.

During the first 2 days headache continued but the vomiting stopped. The clinical impression was that he was improving. However, in the early hours of April 30 he became noisy, irrational, and unmanageable, and was given 10 cc. of paraldehyde intravenously. The spinal fluid was grossly purulent and contained 54,900 leukocytes (mostly neutrophils). There were a few Gram-negative intracellular diplococci which morphologically resembled meningococci. The blood showed 10,550 leukocytes (73% neutrophils; 17% lymphocytes). A diagnosis of meningococcal meningitis was made, and the patient was given intravenously 4 gm. of sodium sulfathiazole (the only available sulfonamide) in 30 cc. of water.

Deep coma developed rapidly. The pupils were small, equal, and reacted to light. The neck was only slightly stiff; Kernig's sign slightly positive. In contrast, there were marked rigidity and orthotonos of the spine; the umbilical and cremasteric reflexes were absent. Knee and ankle jerks were hyperactive but equal, and a bilateral Babinski with fanning was present. No ankle clonus was elicited. Breathing was markedly stertorous, and extreme trismus was present. Five gm. of sulfanilamide were given in 1000 cc. of physiologic saline solution. The breathing became Kussmaul in type, and an alarming pulmonary edema developed despite a strong, full pulse and a blood pressure of 140/85. This edema responded temporarily to oxygen, peripheral tourniquets, venesection, and atropine. At 1 P.M., a cisternal puncture was done in the hope that it would help the dyspnea by lowering intracranial pressure. Although it was not measured, we thought that the cisternal pressure was definitely increased. Five hours later the patient had improved and was given 5 gm. sulfanilamide in 1500 cc. of physiologic saline subcutaneously, as well as 100,000 units of antimeningococcal serum intravenously. In the early evening he became cyanotic and a progressive, severe pulmonary edema developed which failed to respond to any form of therapy, including digitalis intravenously. He died at 2 A.M., May 1, 1943. Cultures of the spinal fluid showed numerous colonies of meningococci which gave characteristic agglutination tests. Cultures of venous blood were negative at the end of 2 weeks. No malaria parasites were found in 4 thick blood films.

The clinical diagnoses were: (1) acute cerebrospinal meningitis due to meningococcus; (2) bronchopneumonia involving the lower lobes of both lungs, etiology undetermined.

PATHOLOGIC EXAMINATION. (Seven hours after death.) The positive findings were confined to the central nervous system and lungs. All other organs were those of a healthy young man. Careful search of specially fixed and stained tissue sections showed no malaria parasites. The pathologic diagnoses were: (1) acute, diffuse, meningococcal encephalomyelitis; (2) acute, purulent, meningococcal cerebrospinal leptomeningitis; (3) edema of brain, marked; (4) confluent bronchopneumonia, all lobes of both lungs, etiology undetermined.

Central Nervous System. The leptomeninges were thin and tightly stretched, and beneath them was a delicate film of creamy, yellow pus, which occupied the Sylvian fissure and the sulci on the lateral and superior aspects of the brain. At the base of the brain, however, and in the cisternæ there was only a small amount of cloudy fluid and no adhesions. The dura mater was hyperemic.

The brain weighed 1550 gm.; the cerebral hemispheres were greatly swollen. The convolutions were broad and flat and almost completely obliterated the sulci. After fixation in 10% neutral formol-saline for 1 week, multiple coronal sections were made of the brain. Numerous clusters of bright red, punctate hemorrhages were scattered throughout the white matter, although the gray matter was mostly spared (Fig. 1). In some places several small hemorrhages

had fused to form larger lesions 5 to 8 mm. in diameter. All the tissues were extremely edematous and hyperemic with wet, boggy, pink cut surfaces. There was no macroscopic thrombosis of the arteries or veins. The ventricles were of normal size and contained thin, cloudy fluid; but there were neither adhesions nor obstruction of the aqueducts. The choroid plexus was covered with fibrinous exudate.

The leptomeninges of the spinal cord contained an increased amount of cloudy, watery fluid, but there were no pockets of pus or adhesions. The pachymeninges were hyperemic. Throughout the white matter of the entire spinal cord were numerous small hemorrhages similar to those in the brain.

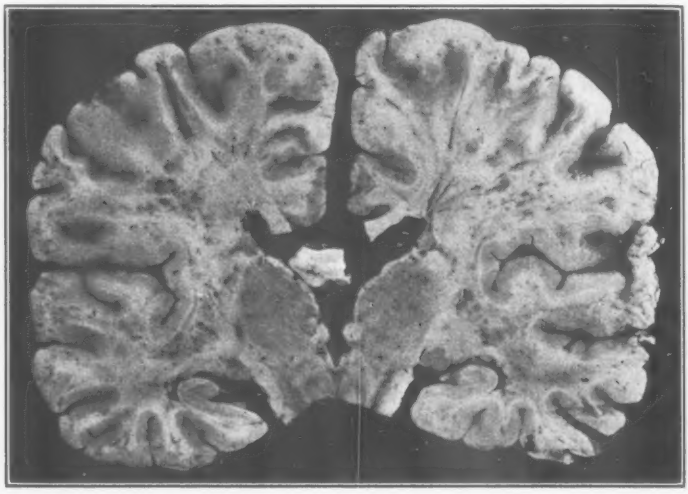

FIG. 1.—Coronal section through the region of the thalamus to show the multiple hemorrhages in the white matter of the brain.

Respiratory System. The right lung weighed 900 gm. and the left lung 800 gm. The entire pleura in both thoracic cavities was covered with a layer of yellowish gray, granular, fibrinous exudate. The lungs cut easily and large amounts of cloudy, reddish gray fluid, containing almost no air, flowed from the cut surfaces. All parts of the lungs were extensively consolidated, except for a few small foci at the apex and along the lower margin of the upper lobes. The tissues were pale reddish gray, finely granular, moderately friable and remarkably uniform, so that the pneumonic lesions appeared to be everywhere of the same age. Frothy, red fluid filled the bronchi, but the mucosa appeared to be hyperemic only. The trachea, larynx and nasopharynx were not affected. The pulmonary arteries and veins were normal. The lymph nodes at the hilum were moderately enlarged, and the cut surfaces were bulging, moist, and reddish gray.

MICROSCOPIC EXAMINATION. *Technique.* Portions of cortex and white matter were taken from the cerebral hemispheres, basal ganglia, pons, medulla oblongata, cerebellum and spinal cord, fixed in 10% formol-saline, embedded in paraffin, cut at 5 μ, and stained with hematoxylin and eosin, van Gieson's and Verhoeff's stains, Mallory's phosphotungstic acid hematoxylin and Goodpasture's bacterial stain. Frozen sections cut at 20 μ were stained for myelin (Spielmeyer) and fat (Sudan III).

Meninges. The cerebral leptomeninges were moderately distended by exudate, which extended into the sulci and for a short distance among the large blood-vessels. This exudate consisted of fluid, much fibrin, and many neutrophils. Lymphocytes, large mononuclears and phagocytes containing

dead leukocytes and cellular débris were present, but there was no organization. The meningeal vessels were strikingly hyperemic, but no thrombi were seen. The dura mater was not affected. The spinal leptomeninges were less diseased; here the exudate was comprised largely of lymphocytes and large mononuclears with only small numbers of neutrophils and little fibrin (Fig. 2).

Brain. The principal lesions were: (1) acute hemorrhagic foci or purpura of the brain and (2) a true acute encephalitis with necrosis. In some regions they occurred in pure form; in others there was a mixture of the 2 types.

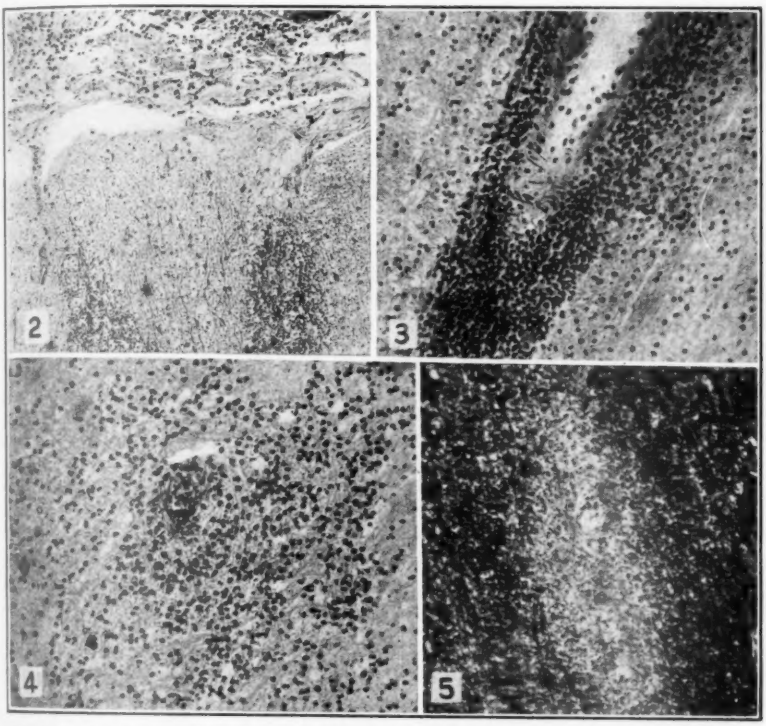

FIG. 2.—Two hemorrhagic lesions in the lateral funiculi of the spinal cord. Note the slight inflammation of the meninges. (Hematoxylin and eosin; × 200.)

FIG. 3.—Perivascular exudation of neutrophils in the cerebral white matter. (H. and E.; × 450.)

FIG. 4.—An area of acute necrotizing inflammation in the white matter of the brain. (H. and E.; × 500.)

FIG. 5.—Area of pallor around a hemorrhagic focus showing displacement of the myelinated nerve fibers by red blood cells. There is no primary demyelination. (Spielmeyer's myelin stain; × 100.)

The hemorrhagic lesions were small foci of recent bleeding scattered widely throughout the white matter of the brain and spinal cord. For the most part the foci were poorly defined and bore no apparent relationship to the arteries or veins. Instead, they were usually situated at some distance from the arteries; they were observed in purest form in the spinal cord (Fig. 2), and in the tissue just adjacent to the lateral ventricles. In other places they occurred either alone or in combination with foci of true encephalitis. The smallest hemorrhages, presumably the freshest, consisted of well preserved erythrocytes, but in the larger ones the red blood cells had undergone conglutination, lysis and a peculiar coagulation necrosis, so that the individual cells were no

longer recognizable. In the relatively few instances where the hemorrhage was perivascular, the earliest change was filling of the affected vessel, often a small artery or arteriole, by conglutinated red blood cells followed by extravasation of erythrocytes into the Virchow-Robin spaces; when these spaces became greatly distended, bleeding into the brain substance took place.

The acute encephalitis was of 2 types, usually quite distinct, although occasionally mixed. These were: (*a*) perivascular exudation; and (*b*) focal inflammation and necrosis of the white matter. The perivascular exudation was conspicuous, being present around both small and large vessels (Fig. 3). The exudate was made up mostly of neutrophils with occasional lymphocytes and large mononuclears, some of which were phagocytes, and small amounts of fibrin. The striking feature of the perivascular lesion was its tendency to remain localized in the space of Virchow-Robin (Fig. 3), which was not only true in solitary lesions but also in many of the places where there was diffuse necrotizing inflammation. In a few places, on the other hand, the inflammation around the arteries fused with the surrounding encephalitis, indicating spread from the vessels to the adjacent white matter.

The second manifestation of the encephalitis was widespread and severe necrotizing inflammation (Fig. 4). This varied from small foci, in which degeneration and early necrosis of the white matter had occurred, to large areas of marked brain necrosis and inflammation. Loss of tissue was often great with resulting condensation of nuclei and a highly cellular appearance. All degrees of nuclear change were observed, including karyorrhexis, pyknosis and dissolution of nuclei. Swelling and chromatolysis were common and when the ganglion cells were affected, bizarre multinucleated forms were encountered. Ameboid microglial cells and neutrophils were present in large numbers.

Many of the small arteries, arterioles and capillaries of the brain contained thrombi of coagulated protein material and conglutinated red blood cells, which often showed a peculiar coagulation necrosis. There was no demonstrable injury to the arterial wall, and the exudate was entirely perivascular.

Sections stained for myelin showed numerous areas of pallor corresponding to the areas of hemorrhage and encephalitis. Careful study of these lesions and comparison with sections stained by other methods showed that the pallor was due to displacement of the nerve fibers by extravasated erythrocytes and inflammatory cells and not to primary demyelination (Fig. 5). Individual nerve fibers could be traced into the pale areas where they were either broken or pushed to one side by the hemorrhage or exudate. It was simply a case of nerve tissue being displaced by other cells.

In the spinal cord the lesions were hemorrhagic. Necrosis and exudation were not observed, and there was no primary demyelination.

Distribution of Lesions. Hemorrhagic as well as inflammatory lesions were found throughout the white matter of both cerebral hemispheres. They were most common in the posterior frontal, parietal and anterior occipital regions. The corpus striatum, thalamus and mid-brain were not as markedly involved and only occasional lesions were found in the medulla oblongata, pons and cerebellum. Inflammatory and mixed type lesions predominated in the white matter surrounding the thalmus and corpus striatum, whereas hemorrhagic lesions were most conspicuous in the frontal and occipital lobes.

The cerebral cortex was largely spared, except for chromatolysis of the pyramidal cells and swelling of the oligodendrial cells. The microglial cells were mostly normal.

The choroid plexus was the seat of an acute purulent inflammation similar to that present in the leptomeninges.

In the spinal cord, throughout its length, hemorrhagic lesions were indiscriminately scattered through the three funiculi of the white matter. The lateral funiculi were particularly affected.

Respiratory System. There was widespread confluent bronchopneumonia, which affected nearly all the pulmonary parenchyma. In contrast to the gross appearance, which was remarkably uniform, the microscopic picture varied considerably. The exudate contained great numbers of neutrophils and small numbers of mononuclears. Fibrin was scanty, was seen in only a few places

and there was no organization. Edema was conspicuous, especially in areas where the pneumonia was spreading, hyaline membranes lined many of the alveoli. Passive hyperemia was marked. The bronchi and bronchioles were plugged with exudate, with inflammation spreading into the surrounding tissues. No hyaline membranes were found in the bronchi, and there was only an occasional focus of necrosis of the lining epithelium. Bacterial stains showed no organisms, but in cultures of the lungs a few colonies of non-hemolytic *Staphylococcus aureus* and *Streptococcus fæcalis lactis*, grew but no meningococci were found.

Discussion.—The striking clinical observations were: the sudden onset of meningitis in a patient thought to be recovering from a mild upper respiratory infection; the fulminating course of the disease; the rapid development of deep coma and stertorous respiration; the marked pulmonary edema which failed to respond to treatment; and the absence of signs of pulmonary consolidation until shortly before death. At autopsy, the inflammation of the meninges was much less than had been anticipated and was certainly not sufficient to have caused death. The noteworthy and unexpected finding was the presence of a widespread, hemorrhagic and necrotizing encephalomyelitis, limited chiefly to the white matter. Confluent bronchopneumonia involved all lobes of the lungs and was of much greater extent than had been supposed from clinical signs. There was no disease of the adrenals.

This case corresponds to those reported by Banks and McCartney,[1] who divided their 10 cases of meningococcal encephalitis into 3 groups on the basis of clinical and pathologic observations. In the first, fulminating encephalitis predominated with signs of purpura, coma, cerebral edema, widespread punctate hemorrhages, capillary thrombosis, and no cellular exudates. Meningitis was absent or minimal. In the 2nd group, cases of acute encephalomeningitis, patients either died within a few days or recovered with transient Parkinsonism. Clinically, the picture was of acute meningitis, complicated by encephalitis (coma, cyanosis, and stertorous, rapid, irregular respiration). Pathologically, there was either hyperemia, hemorrhage, and capillary thrombosis; or an acute exudative inflammation. The 3rd group was chiefly meningitis with focal encephalomyelitis. Occasional massive adrenal hemorrhage was found, but was different from the acute meningococcal infection which involves the adrenal but not the cerebrum or the meninges.

On the basis of both clinical and pathologic features, our case falls into the 2nd group described by Banks and McCartney. The only differences are that myelitis was an important finding, and that there was an extensive pneumonia. Banks and McCartney hold that meningococcal encephalitis is seen most frequently either at the height of an epidemic, when the organisms supposedly are highly virulent and the dose massive; or, in non-epidemic times, at the period of greatest prevalence of the disease. Yet, the present case occurred when there was no epidemic, and in the early autumn, when meningitis was not prevalent.

It is interesting to note that in most of the reported cases 2 distinct lesions have been found in the brain, *viz.*, hemorrhagic and inflammatory. These are seen in pure form as well as in combination. The

reasons for this are not known, but it may be that the hemorrhagic lesions are the counterpart in the brain and spinal cord of the cutaneous rash and purpura, as well as of the adrenal hemorrhage seen in Waterhouse-Friderichsen syndrome.

Myelin sheath stains showed that, although necrosis and displacement of brain tissue produced zones of pallor in the myelin preparations, true demyelination did not occur. The absence of demyelination distinguishes this disease from the cases of acute hemorrhagic leukoencephalitis of Hurst[3] and other rare, primary demyelinating diseases.

The etiology of the pneumonia is not established. It may, of course, have been caused by meningococci; but these organisms were not cultured from the lungs, and could not be demonstrated in bacterial stains of the tissues. Even if meningococci had been isolated, the diagnosis would not have been established, for, in the presence of meningococcal septicemia, the organisms might be cultured from almost any organ. Probably it was a post-infectious pneumonia of some sort, similar to the post-influenzal pneumonias. The rapid development and spread is most likely explained by the marked pulmonary edema which provided both a suitable culture medium and an excellent vehicle for dissemination.

Summary.—This is the report of the case of a young soldier who by clinical examination and laboratory tests appeared to have acute meningococcal cerebrospinal meningitis, with deep coma, difficulty in breathing and extreme pulmonary edema. At autopsy, however, he was found to have had acute encephalomyelitis, violent and extensive, with but comparatively little meningitis. The encephalitis was characterized by purpura of brain and cord and acute necrotizing exudative inflammation, but no demyelination. The case is like those described by Banks and McCartney, but differs in that it did not occur during an epidemic nor at a time when meningitis was prevalent.

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A MUMPS EPIDEMIC IN A SMALL TASK FORCE

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This paper presents a study of a mumps epidemic which occurred in a small Task Force during 1942–1943. Most of the cases were contracted enroute to, and after arriving at, a tropical overseas base. A number of cases occurred in the United States while the Force was in training, but the hospital records of these cases were not available for study. Consideration is given to the effect of variations in housing and

environment upon the spread of the disease; certain clinical manifestations of mumps as it occurred in this Unit are also described.

The elements of this Unit were activated in Louisiana in February, 1941. The first mumps case appeared there in early autumn, and, thenceforth, the hospital was almost never without a case of mumps. The spread of the disease was never remarkable, remaining solely in one company. This isolation is probably explained by the mild weather prevailing in Louisiana and by the fact that troops were housed in tents holding only 4 to 6 men. In February, 1942 the battalion was transferred to another camp. There, the men lived in two-story barracks housing about 65. The number of buildings was inadequate, and crowding was the rule. The weather, too, was generally unfavorable with a coincidental high rate of respiratory infection. At that time an increase in mumps cases was noted; but after consultation with the Camp Medical Inspector, it was decided that no especial precautions need be taken.[1] From April to October, 1942, 22 cases of mumps appeared, mostly from the original focus, Company "A," with 3 cases each developing in Company "B" and Company "C," and 1 in another unit of the Force. One case of German measles occurred, but there were no subsequent cases. In October the Force was transferred, temporarily to a third camp, where, in 3 months, 8 more cases of mumps appeared, strangely enough all in Company "D." Again it is pointed out that this was a period of respiratory infection prevalence.

The final move of the Force was to a Port of Embarkation; and in 2 weeks there, 10 more cases of mumps developed. Whatever individuality the components of the Force had prior to this move was now lost. All Units dined in a common mess hall and, in addition, attended lectures and training films *en masse*. The mixing of troops was further exaggerated during the movement overseas when overcrowding of men became an unfortunate necessity. It was not unexpected, therefore, that an explosive outburst of new mumps cases occurred widely, and, in the following month, a total of 54 cases appeared. Subsequently 28 were transferred to the station hospital, and these, plus 101 others which developed after debarkation, constitute the basis of this report proper.

Incidence. Chart 1 depicts the course of the epidemic and correlates the number of cases with environmental conditions. It is evident that the greatest incidence of cases is closely associated with the inclement weather and overcrowding. At the overseas base, housing conditions were good; there was no crowding; and barracks were constructed to permit four-way ventilation. The climate was favorable during the early months after arrival, and exceptionally few respiratory complaints were noted on sick call. The number of mumps cases reached a peak during the first month after arrival and then precipitously died away.* In a random sampling, 381 men admitted having mumps previously, 187 denied having had mumps, and 13 were doubtful. Why these susceptible men did not contract the disease is conjectural; but it is

* Contact with the local population was not close. To our knowledge, only 1 native contracted mumps.

known that mumps antibody can be demonstrated by complement-fixation tests even without a history of obvious infection.[2] Also, adequate ventilation of barracks may have played a large part in stopping the spread of this infection.[7]

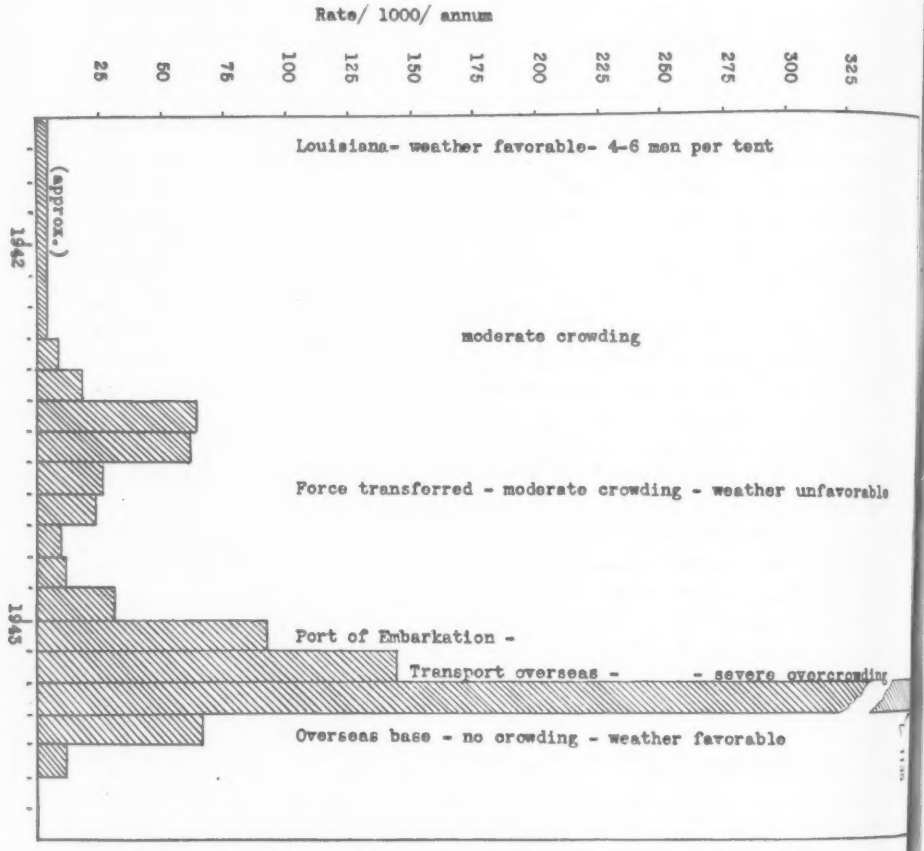

CHART 1.—Incidence of mumps correlated with season and housing of troops.

In this series of 129 cases (126 males and 3 females), the total number of days lost was 2657, which represents a staggering figure, but in keeping with previous experience with mumps in the Army.[5,6] The average hospital days from all causes was 20.2; from mumps and complications referable to it, 19.3 days (102 cases); and from mumps uncomplicated 18.2 days (30 cases).*

The average age of all patients was 24.8 years. Nine men were over 30 years of age.

Eight cases (6%) claimed definitely to have had mumps before, and 2 of these initial attacks occurred under our own observation. One,

* It must be remembered that these figures do not represent days of actual illness, but the time hospitalization was deemed necessary to cover at least the minimum period of infectivity in each case.

treated for bilateral mumps without complication in July, 1942, developed bilateral mumps again in March, 1943, this time with a complicating unilateral orchitis. The 2nd case had bilateral mumps on March 20, 1943 and developed left parotitis on May 14, 1943.[9]

Clinical Manifestations and Course. Few cases presented prodromata. Only 14 of the 129 cases had prodromal complaints, mostly minor and lasting from 1 to 3 days. Six had headaches; 4, sore throat; 2, malaise; 2, abdominal pains; 1, earache; and 1, nasopharyngitis. However, 1 patient was admitted as a malaria suspect, complaining of headaches, fever, chilly sensations, weakness and infrequent cough.* His temperature was 101.8° F.; the leukocyte count, 10,100 (41% lymphocytes). Blood smears for plasmodia were repeatedly negative, and, after 2 days, bilateral parotid pain and swelling established the true diagnosis. Another case was admitted with a temperature of 102.8° F., chills, weakness and severe headache. Malaria, typhoid fever, and atypical pneumonia were considered; and, though chest examination and Roentgen rays were negative, sulfathiazole was given (indication?). Two days later left parotitis became evident. The leukocyte count was 10,000 with 55% lymphocytes.

There was little difficulty in diagnosis. The great majority of cases reported with established parotid swelling; while others, without this, gave a typical story of "my jaw locked" or complained of pain and/or tenderness over the angle of the jaw. Four patients were admitted with testicular complaints alone, and 3 of these, subsequently, developed parotitis. The 4th never presented definite parotid involvement and is included as a mumps case on the basis of the prevailing epidemic, bilateral orchitis, absence of venereal disease or inguinal lymphadenopathy, and a leukocyte count of 7300 with a relative lymphocytosis of 58%.

Uncomplicated mumps ran a smooth course. However, 44† (35%) of the 126 males in this series developed orchitis 6 days, on an average, after the initial complaint. This incidence is higher than the usual 15 to 30% found in other series.[3,8] Physical trauma to the testes has long been accepted as an exciting cause of mumps orchitis. However, strict bed rest alone has been shown not to lower the incidence.[4] Prophylactic support to the testes was done on a few cases, and the impression was that it did not help. This command has consistently had a high venereal disease rate, and the point was raised whether or not the trauma resulting from a gonorrheal infection might lower local tissue resistance and thereby predispose to orchitis. Although a previous epididymitis would be a pertinent factor on which to base conclusions, it was found too difficult to obtain this information; and, instead, a previous history of gonorrhea alone was used. Of the 126 males in this series, a positive history of gonorrhea was given by 54 men. The incidence of orchitis in this group was 31%, while the incidence in those denying previous gonorrhea was 37%. Thus, pre-

* Malarial fever, estivo-autumnal, is hyperendemic at this Post and experience has taught us to suspect malaria in all cases until proven otherwise.

† Includes 1 case of bilateral orchitis without parotitis.

vious gonorrhea may be ruled out as a predisposing factor in mumps orchitis.*

TABLE 1.—GONORRHEA AND THE INCIDENCE OF MUMPS ORCHITIS

	Cases	No. developing orchitis
Previous history of gonorrhea	54	17 (31%)
No previous history of gonorrhea	72	27 (37%)

Orchitis rarely occurs before puberty, which suggests that age may play a part in etiology. The mumps cases were divided, therefore, into those younger than 25 and those older (the average age in the series was 24.8 years). Of the 126 males, 79 were in the younger age group, and 32 (41%) of these developed orchitis. Forty-seven men were in the older age group, and 12 (26%) developed orchitis. Thus, age does not predispose to the development of this complication; and, if any conclusion may be drawn, the younger (more active?) adult seems more disposed.

TABLE 2.—AGE AND INCIDENCE OF MUMPS ORCHITIS

Age	Cases	No. developing orchitis
Under 25	79	32 (41%)
Over 25	47	12 (26%)

Of the 44† cases with orchitis, 25 developed in patients presenting bilateral mumps and 18 from cases of unilateral mumps. Of the 18 cases with unilateral parotitis, 4 developed bilateral orchitis. Of 25 cases with bilateral parotitis, 9 developed bilateral orchitis. This suggests that bilateral parotitis tends to a slightly greater incidence of bilateral orchitis.

TABLE 3.—COMPARISON BETWEEN UNILATERAL AND BILATERAL PAROTITIS IN RELATION TO EXTENT OF SUBSEQUENT MUMPS ORCHITIS

Unilateral parotitis:	
Unilateral orchitis	14
Bilateral orchitis	4 (22%)
Bilateral parotitis:	
Unilateral orchitis	16
Bilateral orchitis	9 (36%)

Six months after recovery, the 44 patients who previously had orchitis received a follow-up examination. Testicular atrophy was noted in 21 (48%), and varied from slight to moderate in degree.

Other complications referable to mumps were: 1 meningo-encephalitis (Case 1) and 1 questionable pancreatitis.

Intercurrent diseases occurred in 28 patients. It included 8 cases of malaria (Case 2), 4 gonorrhea, 3 bronchitis, 3 conjunctivitis, 2 chancroid, 2 nasopharyngitis, 2 tonsillitis, 2 myositis, 1 balanitis, and 1 appendicitis (Case 3).

The average highest temperature in this series was 101° F. Two cases had temperatures of 105.2° F., both with complicating malarial fever. One case each of mumps meningo-encephalitis, bronchitis, and gonorrhea developed 104.8° F.; 27 cases developed temperatures of

* However, all 4 men with intercurrent acute gonorrhea developed orchitis.

† Includes 1 case of mumps orchitis without parotid involvement.

103° F. and higher, with 16 referable solely to mumps; 20 cases had temperatures ranging between 100° and 103° F.; 13 cases showed no elevation in temperature at any time; the majority of cases had temperatures between 98° and 100° F.

Laboratory Data. The average leukocyte count for all cases was 6520 per c.mm.; for the cases presenting intercurrent disease, 7500; and for mumps and complications referable to it, 6210. The highest leukocyte count in this series, 36,000, occurred in the case with intercurrent appendicitis; however, the next two highest counts, 10,250 and 10,100, occurred in cases of uncomplicated mumps. The lowest leukocyte count was 3600.

Lymphocytes averaged 36% in all cases and ranged from 15% to 59%. Only 4 cases showed lymphocytes below 26%, while 5 cases were above 50%.

All urinalyses were negative, except 3. Two showed traces of albumin which accompanied temperatures of 103.2° F. and 104° F. and are considered as febrile albuminuria; the 3rd showed a trace of albumin and a few red cells, but follow-up urinalyses were always negative.

Treatment. Treatment was symptomatic in all cases with results satisfactory throughout the series. Sulfathiazole was given in 8 cases for various indications, and there appeared to be no change in the usual course of mumps or in the incidence of orchitis. This agrees with a conclusion reached in a larger study.[3] None of the orchitis cases was treated surgically.

Report of Cases. CASE 1. Male, aged 25, admitted March 23, 1943 with a complaint of pain of 1 day's duration involving both sides of the face. Past history and family history were non-contributory. Physical examination was normal except for injection of the oropharynx and ostium of left Stensen's duct. Both parotid areas were tender, but no swelling was discernible. Blood study showed: red blood cells, 5,820,000; hemoglobin, 95%; leukocytes, 4250 with 47% lymphocytes. Urinalysis was negative. A diagnosis of mumps was made; and, in a few days, pain and tenderness disappeared completely.

On March 29 the patient complained of severe frontal headache. The temperature was 102° F. and pulse rate, 92. Acetyl salicylic acid and an ice-bag afforded no relief. The temperature rose to 102.4° F., and later to 104.8° F. The pulse rate varied from 80 to 120 and at times was disproportionately slow in relation to the temperature. Slight nuchal rigidity was found which progressed rapidly to complete head retraction and opisthotonos. An occasional convulsive spasm shook the patient and once there was a momentary chill. Projectile vomiting occurred twice within a few hours. Restlessness and delirium became manifest. Neurologic examination revealed the presence of Kernig, Brudzinski and Babinski signs. The superficial reflexes were exaggerated and the deep reflexes diminished. The impression was mumps meningoencephalitis, but serious consideration was given to the possibility of malarial fever, cerebral type. Repeated negative blood smears for plasmodia ruled out the latter possibility. A spinal tap was done, withdrawing 15 cc. of clear, colorless fluid under some increased pressure. The fluid showed no organisms or pleocytosis. The Pandy test was negative. A leukocyte count was 5750 with 34% lymphocytes. The following day, a repeat blood count showed 3750 leukocytes with 58% lymphocytes.

The patient's condition appeared grave, but the spinal tap seemed to relieve him. Sulfathiazole was given empirically, 2 gm. initially and 1 gm. every 4 hours thereafter, in addition to symptomatic treatment. Within 2 days, all abnormal neurologic findings had disappeared and, except for an infrequent

headache and emesis, the patient went on to a complete cure, with discharge to duty on April 15.

CASE 2. Male, aged 33, admitted March 21, 1943, complaining of pain in the right side of the face of 4 day's duration and slight local swelling for 1 day. Physical examination was negative, except for slight swelling, and marked tenderness of both parotid areas. With symptomatic care, the parotitis subsided within a few days. There was no fever at any time.

On March 28 the patient had a temperature of 100° F. and a slight headache. The temperature rose to 105° F. on March 29. Malaise and severe frontal and occipital headache were present. No relief was obtained from ice-caps or repeated doses of acetyl salicylic acid. Beginning mumps meningo-encephalitis was suspected, but neurologic examination at this time was entirely normal. On March 30 slight meningismus and absent cremasteric reflexes were noted, and sulfathiazole therapy was begun empirically. Slight epistaxis occurred 4 times within 48 hours and non-projectile vomiting twice. Lumbar puncture was done, withdrawing 25 cc. of clear, colorless fluid under an initial pressure of 18 mm. of mercury. No bacteria, pleocytosis, or increased albumin were found. A blood count showed: erythrocytes, 5,140,000; leukocytes, 6200; neutrophils, 72; eosinophils, 2; basophils, 1; and lymphocytes, 25. A thick-film blood smear revealed *P. falciparum*, 125 rings per 100 white cells.

Antimalarial treatment was started immediately and sulfathiazole was discontinued. The following day, the patient felt better but continued to suffer an occasional headache for 4 days. The temperature returned to normal on the 5th day, and the patient was discharged from the hospital on April 20, as cured.

CASE 3. Male, aged 23, admitted March 19, 1943, with a complaint of pain, tenderness, and swelling of the right parotid area. Examination was negative, except for the local findings. By March 23, all complaints had cleared.

On March 25 the patient developed abdominal pain, so severe as to demand morphine. Diarrhea was also present and emesis occurred later. The pain began in the right testicle and radiated toward the umbilicus. The testicle was not enlarged but was slightly tender. Abdominal tenderness was most marked in the right suprapubic region. There was no rigidity or rebound tenderness. Attempts to extend the right leg increased the pain. Temperature and pulse rate were normal and a blood count showed: 16,300 leukocytes; neutrophils, 83%; lymphocytes, 17%. A later blood count showed: 20,100 leukocytes; polymorphonuclears, 85%. Urinalysis was negative throughout.

The next morning, temperature and pulse rate were still normal, and a blood count showed: 22,300 leukocytes; neutrophils, 87%. Pain and tenderness were now most marked along the course of the right spermatic cord and lateral to the usual site of the appendix. The pain was more intense than usual in appendicitis. Because of these findings and the recent mumps, a diagnosis of early orchitis with reflex pain along the spermatic cord was considered most likely. However, serious consideration was given to a diagnosis of acute appendicular obstruction, and close observation was continued. That afternoon, the temperature rose to 101.4° F. An erythrocyte sedimentation rate (Wintrobe) was 24 mm. in an hour, and another blood count showed: 36,000 leukocytes; and, polymorphonuclears, 82%. The pain had eased slightly and was now localized in the right lower quadrant. Nausea was present. Examination now showed right rectus spasm, tenderness, and rebound tenderness in the right lower quadrant, maximum over McBurney's point. In view of this new picture, immediate operation was advised.

Acute, suppurative appendicitis was revealed on operation. A fecalith, the size of a date seed, was found impacted at the base of the appendix and the entire organ was inflamed, swollen, and tense, with rupture imminent. The tip was adherent to the lateral wall, which accounted for the atypical location of the early findings. Appendectomy was performed, and, after an uneventful convalescence, the patient was discharged to duty on April 21.

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Summary and Conclusions. 1. A history of a mumps epidemic in a small Task Force is described.

2. The total days lost by hospitalization in the series of 129 cases was 2657. This is a large figure, but is in keeping with previous experience with mumps in the Army.

3. A correlation is evident between inclement weather and crowded living conditions and the incidence of mumps.

4. Few cases presented prodromata, and diagnosis was obvious in the great majority.

5. Orchitis developed in 35% of this series. Neither age nor a history of previous gonorrhea appeared to play a part in the incidence of this complication. One case of mumps meningo-encephalitis and one of mumps orchitis without parotitis occurred.

6. Leukopenia, with a relative lymphocytosis, was present in most cases. Urinalysis was uniformly negative.

7. Treatment was symptomatic with satisfactory results. In 8 cases, sulfathiazole was given and seemed not to affect the course of the mumps.

8. Of 129 cases, 3 are reported in some detail.

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UNDER THE CHARGE OF

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THE USE OF PENICILLIN IN SURGICAL INFECTIONS

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Since penicillin is a powerful chemotherapeutic agent which has a specific effect on the organisms responsible for the majority of infectious lesions commonly classified among surgical diseases, it is becoming apparent that the treatment of many of these diseases may require radical revision. However, there are certain pathogenic bacteria against which penicillin, in concentrations obtainable *in vivo*, is not effective, including the gram-negative bacilli, some of the non-hemolytic streptococci and occasional strains of staphylococci. Thus certain limitations of the drug are already clearly defined. Adequate supportive therapy remains an essential feature in the management of surgical infections and should include operative intervention when indicated.[8]

There have appeared in recent months many reports on the use of penicillin in a variety of infections, although few of them have included enough cases to allow statistically significant deductions to be made. Generally, cases have been classified in terms of their etiologic organisms, for the decision as to whether or not a patient should receive penicillin has depended upon the causative organism and its susceptibility to the drug. Early workers with penicillin showed that the drug is a potent chemotherapeutic agent capable of inhibiting most gram-positive organisms and gram-negative diplococci.[2,7,12] They further demonstrated the lack of effect upon gram-negative bacilli. Abraham and Chain,[1] working with *Escherichia coli*, found that these and other gram-negative bacilli produce a substance which rapidly destroys the bacteriostatic activity of penicillin. They called this substance penicillinase.

Dosage and Administration. Many points of controversy have arisen since penicillin has been available but, because of the limited supply,

* Now on Active Service in the Armed Forces.

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considerably more experience is necessary before they can be conclusively settled. Paramount among these is the question of dosage, which has been heavily influenced by the inadequacies of supply. Because of this, minimal, rather than optimal, amounts have been recommended.

The daily dosage recommended by investigators varies from 40,000 to 400,000 Oxford units.[5,11,21,28] The fact that penicillin is a relatively nontoxic drug[7,37] will probably result in the use of larger doses as supplies increase.

Severe staphylococcal sepsis requires the largest doses among the surgical infections.[5,28] The majority of investigators recommend a total 24-hour dose of approximately 100,000 units;[11,21,25] however, Lyons[28] and Bloomfield *et al.*[5] suggest the use of considerably larger amounts, 200,000 to 400,000 units for the initial therapy. The average range of recommended dosage for other surgical infections varies from 40,000 to 150,000 units per day, although Lyons[28] expresses the view that the treatment of clostridial infections may require a dosage exceeding 400,000 units per day. Mixed bacterial infections which frequently contain saprophytic gram-negative bacilli do not appear to respond as promptly or as uniformly as infections yielding pure cultures.[11] Larger dosage may be required to bring these lesions under control.

Since it is possible to demonstrate *in vitro* that organisms growing in low concentrations of penicillin may develop fastness, it appears that adequate initial therapy to obtain a rapid response is indicated.[5]

The clinicians working with penicillin agree that the administration of continuous intravenous infusions of the drug is indicated in all severe infections in which the mortality is high. Herrell[20,21] has demonstrated that a low dosage is more efficient if given by continuous infusion, and has utilized this route of administration throughout the course of treatment in many of his cases. Others feel that the intramuscular route of administration is preferable after the patient has made a satisfactory response to the initial intravenous therapy.[5,11,25,28] Besides the technical difficulty encountered in maintaining any continuous infusion into a vein, there is the troublesome feature of venous thrombosis at the site of injection which not only complicates administration, but may be quite painful. Herrell's[21] experience with venous irritation from glucose solution seems justified; however, it is impractical to use isotonic saline solution exclusively for fear of producing disturbances in electrolyte balance. Alternating diluents of normal saline and 5 per cent glucose in distilled water have been used most successfully. The size of the needle, its insertion into the vein, and the length of time a vein is used are all important features of technique. It has been recommended that 18-gauge needles inserted up to the hub in a fresh vein each day be used. After determining the amount of intravenous fluid a patient can tolerate, the daily dosage should be dissolved in this amount of fluid so that the rate of administration is constant.

For all patients who need systemic therapy and who do not require intravenous treatment, the use of intramuscular injections every 2 to 4 hours is commonly used. The more frequent injections may be preferable.[15] It is wise to use the larger muscle masses, rotating injections from one part to another to assure complete absorption and to avoid repeated local trauma.[25]

If intravenous therapy is indicated, and if for any reason veins are not available for venepuncture or cannulization, bone marrow infusions may be used according to the technique of Tocantins.[40]

The use of local therapy will be included under individual headings.

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Lt. G. F. Schmidt[38] adequately reviewed the literature on the pharmacologic properties of penicillin and the types of toxic reactions in the May, 1944, issue of this journal.

Acute Infections. BACTEREMIA. *Staphylococcal.* Penicillin is the most effective agent available for the treatment of staphylococcemia. The mortality from this disease prior to the use of sulfonamides was about 85%. With sulfonamide therapy the mortality was reduced to about 70%. In the report of Keefer *et al.*[25] in August, 1943, the mortality in 91 cases treated with penicillin was 37%, but this series included patients who were inadequately treated during the early trials of this new drug and 9 cases of acute staphylococcal endocarditis in which the mortality continues to be high. Lyons[28] later reported 9 cases with 3 deaths. More recently, Dawson and Hobby[11] published a series of 18 cases with a mortality of 16.7%, and Herrell[21] reported 14 cases with only 2 deaths (14.3%). These latter figures should give a more adequate answer regarding future mortality in staphylococcemia with the use of penicillin.

Any patient with staphylococcal bacteriemia should receive adequate penicillin therapy at the earliest possible moment and preferably by continuous intravenous infusion.[5,11,21,25,28] It is important to determine promptly the source of the infection, and either excise or drain it surgically or institute other forms of adequate local therapy as indicated.[23]

The rapid subsidence of the severe staphylococcal toxemia after 8 to 72 hours of treatment is one of the most dramatic responses to penicillin therapy.[15] Objectively, patients appear much better even though their temperature and white blood cell count remain elevated. The Florey[15] have emphasized the importance of following the patient and not the chart. In these and other acute infections, the red blood cell count may be suppressed by the action of toxins on the bone marrow, but with inhibition of the parasitic organisms and the subsequent elimination of toxicity, the bone marrow will often respond to demands. Florey and Florey reported several cases in which there was a rapid rise in the hemoglobin following the institution of penicillin therapy.[15] This, of course, does not exclude the use of blood transfusions when indicated.

Acute Hematogenous Osteomyelitis. Acute osteomyelitis is commonly associated with bacteremia, even though positive blood cultures may not always be obtained. The mortality in acute staphylococcic osteomyelitis is considerably lower than that in staphylococcic bacteremia resulting from soft tissue foci. With the use of sulfonamides, the reported mortality of this disease has fallen to levels ranging from 0 to 10%. Hoyt, Davis and Van Buren[22] reported 8 cases treated with sulfathiazole with no deaths. More recently, Baker, Schaubel and Kuhn[4] reported 56 cases treated with sulfonamides with only 1 death. Results of treatment with penicillin have not been universally successful, but this is at least partially explained by the fact that initiation of this form of therapy has been only after adequate sulfonamide trial and failure. Due to the greater potency of penicillin the response should be more rapid than with sulfonamides.[2]

Since the advent of sulfonamides, the practice of early surgical drainage in acute osteomyelitic lesions has been subjected to question. Hoyt, Davis and Van Buren[22] first demonstrated the value of aspiration or non-surgical drainage when the sulfonamides were employed. Recently Baker, Schaubel and Kuhn[4] ran a comparative series of sulfonamide treated cases with surgical drainage and needle aspiration which showed that fewer draining sinuses remained when non-surgical methods were employed. This should also be true with the use of penicillin, which

offers the additional feature of local treatment into the abscess cavity after aspiration.[20]

Beta Hemolytic Streptococcic Bacteremia. With the use of sulfonamide therapy this disease develops less frequently and results in a lower mortality than staphylococcemia. However, the response to treatment may be more prompt with the use of penicillin since comparative *in vitro* studies show it to be more potent than the sulfonamides.[13] Streptococci are more sensitive to the effect of penicillin than staphylococci which permits adequate clinical response with somewhat lower doses.[25] Intravenous therapy is indicated in all types of bacteremias.

Suppurative Infections of Natural Body Cavities. *Empyema.* Sulfonamides have lowered the incidence of empyema following pneumococcal pneumonia, but are inadequate in the treatment of pneumococcic empyema since the presence of large numbers of bacteria of pus and tissue autolysates definitely reduce the effectiveness of these drugs.[27] Penicillin, on the other hand, is not inhibited by these substances[15] and is the drug of choice in the treatment of pneumococcic, staphylococcic, streptococcic and mixed types of empyemata which do not include a predominance of gram-negative bacilli. After the aspiration of pus, local penicillin instilled into the abscess space may be adequate to control completely the infection without the necessity of systemic therapy if the infection is well localized. By these means it is usually possible to avoid surgical drainage. The daily instillation of 25,000 to 50,000 units of penicillin is recommended.[25,39]

Tillett, Cambier and McCormack[39] have reported success in 1 case of pneumococcic empyema following a single instillation; however, 5 to 10 days of treatment is usually required. The pus is frequently sterile after the first or second administration of the drug and subsequently becomes thinner and decreases in amount. The accumulation of thick fibrinous material may necessitate thoracotomy.[25] The response to treatment of empyemas with mixed flora has been considerably slower than in those cases which yield a pure culture. Penicillin should not be used as an irrigating solution in empyema since 6 to 8 hours' contact is required to obtain bacterial stasis.[25] If irrigation is to be performed, it is best done with normal saline. With open surgical drainage of an empyema cavity the usefulness of penicillin sharply decreases since it tends to leak through the wound. If possible, it is wise to avoid surgical drainage.

Suppurative Arthritis. Acute staphylococcic, streptococcic, gonococcic, pneumococcic and meningococcic suppurative arthritis should be treated in the same manner as empyema. Systemic therapy is not required unless there are other active foci. The dose required is small, 5000 units instilled after aspiration being adequate.[25]

Meningitis. Secondary suppurative meningitis caused by pneumococci, staphylococci and streptococci should receive penicillin systemically and locally instilled into the spinal fluid.[25] Rammelkamp and Keefer[36] demonstrated the failure of penicillin to appear in the spinal fluid following systemic administration. This work has been further established by Pilcher and Meacham.[33] These infections should be considered surgical, as they are most frequently secondary to suppurative lesions located in the mastoids or paranasal sinuses. Every attempt should be made to drain these cavities of purulent material, after which penicillin solution containing 250 to 500 units per cc. may be instilled into the cavity at frequent intervals.[15] The importance of the use of intracisternal or intraspinal therapy in combination with systemic treatment is clearly apparent.[33]

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Suppurative Pericarditis. Acute suppurative pericarditis produced by pyogenic cocci should receive systemic penicillin therapy. Surgery may be avoided in some cases by frequent aspiration of pus from the pericardial sac followed by the instillation of 5000 to 20,000 units of penicillin, depending upon the amount of pus removed, and the size of the cardiac shadow on Roentgen ray.

Peritonitis. In peritonitis, penicillin is not usually indicated since penicillinase-producing coliform organisms are generally present.[26] In cases in which pyogenic organisms occur without gram-negative bacilli, penicillin may be useful and should be administered both systemically and locally as indicated.

Abscesses. *Carbuncles and Furuncles.* These staphylococcal infections may be aborted in the early stages of development with systemically administered penicillin.[15] But once necrosis has taken place, pus and necrotic tissue should be evacuated by either surgical drainage or aspiration. If aspiration is employed, locally injected penicillin is recommended.[20]

Visceral Abscesses. These lesions, whether located in the brain, the lung, the mediastinum or other structures, should receive systemic treatment. Liver abscesses usually do not respond to penicillin, since these lesions usually contain coliform organisms. Penicillin is concentrated in the bile,[35] which should make it of use in pyogenic biliary tract infections which do not contain penicillinase-producing organisms.

Localized Wound Infection. *Cellulitis, Lymphangitis and Lymphadenitis.* These infections will usually respond to systemic penicillin therapy. If there is extensive cellulitis and lymphadenitis which results in localized necrosis, surgical or non-surgical drainage is recommended.

Cellulitis of the Face. Septic cavernous sinus thrombosis, periorbital and retro-orbital cellulitis, cellulitis of the nose and cellulitis of the lip usually respond dramatically to penicillin. In septic cavernous sinus thrombosis mortality was almost 100% before the use of sulfonamides with only an occasional recovery.[17] The sulfonamides have reduced the mortality to some degree, but penicillin should be even more effective. These patients should have systemic therapy administered intravenously.[25] The use of anticoagulants such as dicoumarin and heparin is recommended as a supportive measure.[17]

Burns. The importance of burns and their care has been accentuated by the frequency of these wounds in modern warfare. It is most important to prevent pyogenic infection in the superficial burns, for they may be converted into deeper wounds resulting from loss of epithelial structures. Gentle cleansing and application of pressure dressings have been established as the local treatment of choice.[3] Locally supplied sulfonamides in ointments to burn surfaces have left much to be desired.[32] Clark *et al.*[9] reported in *The Lancet*, 1943, 54 burns and scalds in varying stages of healing which had hemolytic streptococci on their surfaces. These organisms had been particularly troublesome in their burn ward. In 41 cases (76%) streptococci disappeared within 5 days with the use of penicillin in a Lannette Wax cream base applied to the surface. All cases showed some improvement. Staphylococci, likewise, disappeared quickly. No toxic effects were noted. *E. coli*, *B. proteus* and *B. pyocyaneus* were not affected. Keefer *et al.*[25] recommended the use of locally applied penicillin to prepare granulation surfaces for grafting. Bodenham[6] reported that streptococci are present in 30 to 80% of the cases he had seen. *Staphylococcus aureus* was present in 100%. He used penicillin in a Lan-

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nette Wax cream base as an ointment and in combination with sulfanilamide as a powder. By the use of the cream preparation it was possible to eliminate streptococci and staphylococci from all surface wounds and hasten the time of grafting. The Lannette Wax cream proved more effective than the powder, which occasionally gave pain. It is usually unnecessary to administer systemic penicillin for locally infected burns unless there is evidence of uncontrolled spread of infection, metastatic infection or bacteremia.

Wounds. Penicillin has been tried in war wounds of all types. Most of the literature now available is concerned with local therapy; but a recent report by Florey and Cairns[14] emphasizes the advantage of combined systemic and local therapy in severe wound infections, for, in any spreading cellulitis or invasive infection, the presence of a bacterial inhibitory substance in the blood stream is of greater value than is an agent applied topically to a wound containing varying amounts of slough. This was adequately demonstrated by Lyons[28] working at the Halloran General Hospital with infected war wounds. As in burns, the drug may be applied in an ointment, as wet dressings or in a powder. Pulvertaft[34] reports good results with the use of local penicillin in wounds. He feels that it is most important to explore and to drain any deep pockets of pus. He used penicillin in a powder, a spray and wet dressings. He too supports the view of Bodenham[6] that, while the gram-positive organisms disappear rapidly, the gram-negative organisms may appear in even greater numbers. Jeffrey[24] corroborates the statements of Pulvertaft, and feels it is essential to maintain drainage. He did not think that the presence of gram-negative organisms significantly delayed healing.

In their report of their experience in North Africa, Florey and Cairns[14] state that ointments and powders were not as successful as instilled solutions or wet dressings. Chronic sepsis of compound fractures responded to systemic therapy if loculated abscesses were not present. One hundred and seventy-one dirty wounds were treated locally with solutions of penicillin. Of them, 53 were sutured around rubber tubes, permitting local use of a solution containing 250 units of penicillin per cc. Complete healing occurred in 104 of the 171 cases, whereas 60 healed in part by granulation tissue, and 7 failed to heal. Healing took place even though the wounds contained *B. pyocyaneus*. The hospital stay was shortened by 3 to 6 weeks. In the prophylaxis and treatment of infection in compound fractures of long bones, those of the femur gave the poorest results. They felt that systemic treatment was inadequate in dosage and duration.

Brain wounds 3 days old or older were excised and sutured. A fine rubber tube was led through a stab hole into the cavity which was irrigated for 4 to 5 days with a solution containing 250 units per cc. The average amount used in each case was 15,000 units. Of 23 cases treated, 3 patients died. Wound healing was by first intention in 6 cases, while in 13 there was slight gaping of the wounds. Temporary sinus formation was common. Small osteomyelitic foci tended to prolong drainage of the wound. Thus it appears that in cases where the drug can be brought into adequate contact with the causative organism, whether saprophytic or tissue invaders, the results are beneficial.

Mary Florey and Williams[16] recently reported in *The Lancet* a comparative study of 212 hand infections. About half of these were treated with local penicillin, and others treated by other means. Both groups received adequate surgical care. Penicillin-treated cases seemed to show an earlier regression of infection than the non-treated cases. Pus was

scanty or absent in the treated cases. Tissue destruction was stopped, pain relieved, and the number of dressings required were reduced in the treated cases. In comparison with the infections treated by the other means, the healing time of those treated with penicillin was considerably shorter. Bone lesions responded equally as well and healed with regeneration of bone. It was possible to start active motion of the penicillin-treated hands much earlier. Locally applied powdered calcium salt was somewhat painful. It was estimated that in 35 of the penicillin treated cases, a total saving of 1000 man days was accomplished as compared to a similar number of control cases.

Clostridial Infections. There is considerable controversy about the value of penicillin in the treatment of clostridial infections. It was recognized by the early investigators that penicillin *in vitro* was capable of inhibiting these organisms.[2,7] Since these infections are so varied, it will be difficult to evaluate the place of any agent in a short period of time. This type of infection is frequently suspected and diagnosed, but errors in diagnosis are often made. The striking difference in morbidity and mortality between clostridial cellulitis and clostridial myositis was recently pointed out by MacLennan.[29] In experimental work with *Clostridium welchii* infections, penicillin is superior to the sulfonamides, as shown by Hac and Hubert.[18] McKee, Hamre and Rake[30] demonstrated that tyrothricin was more effective than penicillin when applied locally to these organisms. It was the opinion of Lyons[28] that proteolytic clostridia recovered from war wounds required 4 to 5 times as much penicillin as do staphylococcal wound infections. The presence of these organisms indicates devitalized tissue or necrotic bone fragments.[28] Lyons highly recommends concentrated local therapy in conjunction with systemic treatment. Florey and Cairns[14] treated 7 cases of gas gangrene, 3 of whom died. Jeffrey[24] was disappointed in the use of penicillin locally in gas gangrene. Cutler[10] reported on 4 patients with major compound fractures who were treated with penicillin systemically and who developed gas gangrene which necessitated amputation. Recently Harvey and Meleney[19] reported the treatment of 2 cases with penicillin, 1 infected with *Clostridium sordellii*, another with *Cl. welchii*, both of whom died. All of these investigators emphasize the necessity of giving sufficient specific antitoxin to patients with these infections, for penicillin will in no way alter the free circulating toxin. At best, it would only inhibit the organisms elaborating these substances. The treatment of anaerobic streptococcal infections has not been adequately investigated up to this time.

Chronic Infections. Penicillin should have great usefulness in the field of chronic surgical infections which include such diseases as bronchiectasis, multiple and single lung abscesses, chronic osteomyelitis and probably actinomycosis.

The treatment of chronic osteomyelitis with penicillin requires surgical removal of infected granulation and fibrous tissue, bone and sequestra in conjunction with systemic penicillin treatment, if improvement is to be more than temporary.[8]

Some strains of *Actinomycosis bovis* are inhibited *in vitro* by penicillin. Actinomycotic lesions may be arrested or completely cured with the use of penicillin in conjunction with surgical excision. The results are encouraging in the cases treated, but considerable time must pass before they can be classified as cured.

The use of penicillin in ulcerative colitis is of doubtful value, though a few patients have shown temporary improvement.[25,41]

Prophylaxis. Penicillin may be useful in preventing postoperative infections. It may be useful in the prevention of infection in traumatic wounds, but adequate studies are not available at the present time. Florey and Cairns[14] state: "There is little doubt that the prevention of infection with pyogenic cocci or its control in war wounds is within reach."

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OPHTHALMOLOGY

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TOXOPLASMIC CHORIORETINITIS

By H. P. Wagener, M.D.

The rather recent discovery that the Toxoplasma, a genus of highly organized protozoan parasite, can invade the tissues of the eye and cause destructive lesions of the choroid and retina has introduced further com-

plexity into the etiologic study of chorioretinal disease. To most, if not to all, ophthalmologists the determination of the causative factor in any individual case of acute, subacute or inactive choroiditis has always been a difficult problem. To the earlier and more commonly recognized sources of ocular infection, syphilis, tuberculosis, the acute infectious diseases and blood stream infections, there have been added in the course of the years focal infections, sarcoidosis and brucellosis. And yet the true etiology of many cases remains obscure. In most instances in which the lesions were discovered during infancy and in many of those seen in early childhood, especially when the lesion was seen in the inactive stage, the rather vague diagnosis of congenital maldevelopment or intra-uterine inflammatory process has been made. The demonstration that certain of these lesions in infants are due to Toxoplasma infection, which, as Pinkerton and Henderson[12] suggest, must occur prenatally as the result of latent or subclinical infection in the mothers, makes it imperative that all of these infants be studied more carefully from the standpoint of the associated presence of intracerebral calcification and the possible presence in the blood of Toxoplasma antibodies. The implied fact that adult infection by Toxoplasma must occur suggests also the necessity of including tests for toxoplasmosis in the routine study of cases of chorioretinitis of obscure etiology.

According to Wolf and Cowen,[20,21] Levaditi[8] and his co-workers in 1928 were able to produce a severe inflammatory reaction in the eyes of rabbits by direct inoculation of emulsions of brain tissue infected with Toxoplasma. "There was intense iridocyclitis, destruction of the cornea, accumulation of exudate containing parasitized macrophages in the anterior and posterior chambers and perivascular infiltration about the papilla. Encysted Toxoplasma were found in retinal neurones. In some instances the central nervous system became secondarily infected, possibly by extension along the optic nerves." In a few rabbits extension of the infection along the optic nerves was observed after cerebral inoculation. No definite statement was made as to the involvement of the eye by this mode of extension.

According to Koch and his co-authors,[6] Hepding[4] in 1938 reported the occurrence in a cock of spontaneous toxoplasmic chorioretinitis resembling that later observed in man. Along with mild upper respiratory symptoms, chemosis of the left conjunctiva and cloudiness of the cornea developed. Histologically, the eye showed a widespread necrosis of the retina around the optic nerve with smaller foci of necrosis in the middle third of the retina. The peripheral part of the retina was infiltrated by large mononuclear cells. There were some swollen, large mononuclear cells and fibrin in the posterior part of the vitreous. The uveal tract was infiltrated by lymphocytes and plasma cells. The optic papilla was intensely infiltrated by round cells and fibroblasts. Single Toxoplasma and cystic forms were present in the lesions.

Probably the first case to be recorded in which Toxoplasma were demonstrated in the tissues of the human eye was that reported by Janku[5] in 1923. A boy, 11 months old, was observed to have a small left eye when 3 days old. At about 3 months of age he was thought to be blind. He developed hydrocephalus and later convulsive seizures. In the macular region of each eye was an area of retinal and choroidal atrophy with marginal pigmentation. There was apparently secondary optic atrophy and some question of elevation or detachment of the nasal peripheral retina in the left, partially microphthalmic eye. The child died, probably at the age of 16 months. Quoting from Wolf and Cowen's summary:

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"At autopsy an enormous internal hydrocephalus due to blocking of the aqueduct of Sylvius was present . . . . The eyes showed chronic inflammatory and productive changes in the choroid and retina in the macular region producing the ophthalmoscopic picture of a coloboma. Sporocysts, which the author considered to be sporozoa, were found in the retinal lesion in the right eye. Huge vacuolated mononuclear cells in one part of the lesion in the left eye were thought to be of parasitic nature and related to the sporocysts in the other eye. This protozoan infection was considered to have been transmitted *via* the placenta into the arterial system of the choroid causing a chronic inflammatory process in the latter with secondary changes in the retina. A hyperplastic tumor-like formation of the left eye was felt to be due probably to the influence of the infection on the course of embryonic development." The parasite in this case, though probably Toxoplasma, was not so identified by the author.

A case, which was regarded by the authors as essentially identical with that of Janku and in which parasites were found which were later identified as Toxoplasma, was reported in 1937 by Wolf and Cowen[19] under the title, "Granulomatous encephalomyelitis due to an encephalitozoan." A child, aged 24 days, had convulsive seizures and what appeared to be active areas of chorioretinitis in each eye, and a healed area of chorioretinitis in the right eye. The maculas were not involved apparently. The child died at 30 days of age. Histologically, the pathologic picture in the central nervous system "consisted of a widely disseminated encephalomyelitis in which the severest lesions were associated with necrosis and caseation primarily in the periventricular gray and white matter, and to a lesser degree in the cortex of the cerebrum. Miliary granulomas scattered throughout the central nervous system were a striking feature of the process. . . . . A localized chorioretinitis was present in each eye, and here as in the brain, necrosis and caseation occurred in the affected areas." Judging from the detailed description of the histologic findings it would appear that the lesions, especially the evidences of edema and necrosis, were more marked in the retina than in the choroid and were especially severe in the inner layers of the retina. The parasites also were found in greater numbers in the retina than in the choroid.

In brief, histologically, foci showed centrally total necrosis of almost all the retinal elements, with marked swelling of the retina in places. Only cellular débris and scattered plasma cells and lymphocytes remained. The retinal pigment epithelium was disrupted with a dispersion of the pigment into the surrounding tissues. In the retina about the necrotic zones, the nerve fiber, ganglion cell and internal molecular layers were edematous and infiltrated by plasma cells, lymphocytes, occasional eosinophils and lipoid laden phagocytes. The ganglion cells were missing or degenerating. The deeper retinal layers showed edema with some infiltration by lymphocytes, neutrophils and monocytes. Some cellular exudate was present on the surface of the internal limiting membrane of the retina with some tendency to infiltrate into the vitreous. Edema and infiltration like that in the retina were present in the choroid, chiefly in the inner layers. There was hyperplasia of the endothelium of many of the vessels of the choriocapillaris. The pial and arachnoidal sheaths of the intra-orbital portion of the optic nerve were infiltrated by monocytes, lymphocytes and plasma cells and there was some extension into the substance of the nerve. Parasites were not found in these last lesions.

The first case observed clinically in which the parasites found microscopically in the lesions were proven definitely by animal inoculations to

be Toxoplasma was reported in 1939 by Wolf, Cowen and Paige.[21] This was an infant taken ill at 3 days of age with convulsive seizures, disturbances in respiration and symptoms of spinal cord involvement. The infant died at the age of 31 days. "Terminally, irregular reddish brown areas were observed ophthalmoscopically in each macular region." The infant had a left Horner's syndrome, deviation of the eyes to the right, and nystagmus to the right. According to Koch and his co-authors, it was thought clinically that these macular lesions were hemorrhages resulting from cerebral birth trauma. At necropsy, however, there was found a widespread encephalomyelitis characterized by focal areas of inflammation and necrosis and by disseminated miliary granulomas. Histologically, the lesion in the right eye proved to be a localized chorioretinitis. A protozoan morphologically identical with Toxoplasma was present in all the lesions.

In 1941, Sabin,[13] who, in 1937, in association with Olitsky, first demonin a guinea pig the occurrence of Toxoplasma in North America, reported 2 cases of encephalitis in children in which the Toxoplasma were definitely established as the etiologic factor. The mode of infection was not established. He did not observe retinal or choroidal lesions in either of these cases. At that time Sabin seemed to think that the only accurate method of diagnosis was by inoculation of the spinal fluid or heparinized blood, or both into mice or guinea pigs by the intracerebral or intra-abdominal routes. He stated that, prior to his 2 cases, "There is therefore definite evidence of toxoplasmic infection in only 1 human being, an infant with 'congenital' encephalitis; that the 4 other cases of congenital encephalitis associated with morphologically similar parasites are also examples of the same infection can be considered only as probable."

Sabin stated that the Toxoplasma might perhaps be found in direct examinations of the spinal fluid "in rare cases in which the disease is especially destructive to the nervous system, as in infants during the first days or weeks of life." He also stated that neutralizing antibodies against Toxoplasma apparently develop in human serum and may disappear as early as 6 weeks after the onset and that the presence of such antibodies would be strong evidence of toxoplasmic infection, which their absence would not exclude. Apparently these neutralizing antibodies may persist in the blood serum for a much longer period of time than was originally supposed since the diagnosis of toxoplasmosis has been established presumably in more recent cases by the presence of these neutralizing antibodies long after the probable onset of the disease.

Also in 1941, Pinkerton and Henderson[12] reported 2 cases of adult toxoplasmosis proven by animal inoculation. These were instances of acute febrile exanthematic disease closely simulating Rocky Mountain spotted fever and endemic typhus and having some features in common with certain of the atypical pneumonias. No mention is made of involvement of the eyes. They suggested as possible diagnostic procedures to aid in the establishment of the diagnosis skin biopsies, neutralization tests, spinal fluid examinations, examination of blood smears, blood cultures, and examination of the sputum in cases with lung involvement. The authors suggest the tick as a possible vector of the disease.

In October, 1942, Sabin[15] reported the results of toxoplasma neutralization tests performed on sera from 151 selected individuals. The sera of 59 of these were found to be positive. Of a group of 13 children ranging in age from 1 day to 15 years who exhibited "cerebral calcification and/or chorioretinitis in the macular region associated with hydrocephalus, micro-

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cephalus and/or convulsions, psychomotor disturbance, etc.," 10 showed positive sera, and 8 of 10 mothers of this group had positive sera. On the other hand, of a group of 10 children ranging in age from 9 weeks to 5 years, who showed "hydrocephalus or microcephaly without cerebral calcification or chorioretinitis," none had a positive serum, and only 1 of 4 mothers of this group examined had a positive serum. And of a group of 9 children ranging in age from 1 day to 5 years who had "convulsions, psychomotor disturbances, etc., without cerebral calcification or chorioretinitis," only 1 had a positive serum. One of 2 mothers of this group had a positive serum. Of a group of 10 patients with "chorioretinitis of unknown etiology resembling that seen in congenital toxoplasmosis," 9 had positive sera. These patients ranged in age from 8 years to 59 years. Of the sub-group of 4 in which the disturbance of vision had been noted first at the age of 5 or 6 years, all 4 had positive sera, as did their mothers.

In November, 1942, Levin and Moore[9] reported a case of fetal toxoplasmic encephalitis. A boy, aged $3\frac{1}{2}$ months, had convulsions, mental retardation, microcephaly and several areas of cerebral calcification. The ocular fundi were thought to be normal. However, 2 months later, "The fundi showed pallor of the nasal portions of both optic disks and several large areas of old chorioretinitis. These were located in the lower temporal portion of the right fundus and in the upper temporal and lower nasal portions of the left. They were all sharply outlined and showed yellowish white patches with accumulations of pigment, chiefly at their margins, but also within the atrophic areas. The vitreous was clear and there were no hemorrhages or areas of edema in the retina." The blood from both the patient and his mother gave positive complement fixation tests for Toxoplasma, but did not contain Toxoplasma neutralizing antibodies. Sabin, who performed these tests, was not willing to accept these tests as unequivocal evidence of toxoplasmic infection.

In January, 1943, Crothers[1] reported a group of 10 cases presumed to have toxoplasmic infection. Among this group were included 7 children with chorioretinitis, convulsions and cerebral calcification. All of these children and all but 1 of the mothers (and this one was not tested) had Toxoplasma neutralizing antibodies in their blood serum. The ages of all the cases were not noted; the ages given were $4\frac{3}{4}$, $10\frac{1}{2}$ and 12 years. No details of the chorioretinal lesions were described.

In January, 1943, Koch, Wolf, Cowen and Paige[6] reported 6 cases of toxoplasmic encephalomyelitis with ocular lesions in which the diagnosis was made on the basis of the clinical findings and was confirmed by the identification of neutralizing antibodies to Toxoplasma in the serum of all the cases. They called attention to the syndrome characterized by chorioretinal lesions, symptoms and signs of widespread involvement of the central nervous system, convulsions, frequently internal hydrocephalus, and cerebral calcification visible in roentgenograms of the head. The ages of the patients in this series ranged from 31 days to 11 years. The chorioretinal lesions were active in 2 patients, aged 31 days and 4 years respectively. In the latter case, the lesions were largely healed but a lesion in the left eye still showed some signs of activity. The lesions in the infant of 31 days, which were actively progressive when first observed, seemed to have become quiescent after 5 months of observation. The lesions were apparently multiple in all except 2 eyes. The macular region was involved apparently in all but 1 of the 12 eyes described. Of the 12 optic disks described, 4 showed simple optic atrophy, 2 secondary optic atrophy, 3 pallor without atrophy, 2 papilledema, and only 1 was normal. All 6 of

the children had strabismus, in 5 convergent, in 1 divergent. Three had searching nystagmus. Three eyes in 2 cases were said to be "small" and 1 in another case was described as microphthalmic. Pupillary membrane remnants were observed in 3 eyes, posterior cortical cataract in 1, and posterior lenticonus in 1. Cerebral calcification was noted in the roentgenograms of the head in 5 of the patients.

Koch and his co-authors include in their discussion another case previously reported by Wolf, Cowen and Paige,[21] in which there was progressive hydrocephalus and small areas of calcification in the brain. The child died at 9 weeks of age. Both eyes appeared to be smaller than normal in size and showed ophthalmoscopically a large, apparently vascularized "membranous mass" posterior to each lens. This was considered clinically to be either a detachment of the retina, a persistent tunica vasculosa lentis, or a glioma of the retina. Microscopically, the masses proved to be toxoplasmic chorioretinitis with masses of partially organized granulation tissue extending into the vitreous from the retina.

Histologically, all the lesions described by Koch and his co-authors were in the active stage. (All of these patients were infants, less than 3 months of age.) There were focal areas of edema and necrosis of the retina, involving in some places all, and in others some of the layers of the retina. The marginal zones of the necrotic areas showed perivascular and diffuse infiltration by lymphocytes, plasma cells, and occasional polymorphonuclear cells, eosinophils, and lipoid laden phagocytes. There was some infiltration and vascular and connective tissue proliferation into the vitreous. The retinal pigment epithelium was disrupted and some pigment cells tended to migrate into the retina. The choroid was moderately infiltrated by cells similar to those in the retina in areas corresponding to the retinal lesions, and the sheaths of the optic nerves were similarly infiltrated. "Toxoplasmas were present in the retinal lesions and in general were most frequent where the lesions were most severe. Occasional parasites without accompanying reaction were observed in relatively normal portions of retina near the margins of inflammatory foci. They occurred singly or in clusters, free or intracellularly, or as 'cysts.' They were were rare in the choroid."

With reference to the pathogenesis of the ocular lesions, Koch and his co-authors believe that the disease has its inception during fetal life, and that the parasite probably reaches the brain and other organs by way of the fetal circulation from the placenta. They think it possible but not likely that, after the brain has been infected, the infection passes by way of the subarachnoid space in the optic nerve sheaths to the interior of the globe. They think that the presence of the chorioretinitis during intrauterine life may interfere with the normal development of the eye since microphthalmos and other congenital defects occur. But this interference must take place rather late in the period of gestation since no major malformations of the eye or nervous system have been found.

Koch thinks that the earliest phase of the chorioretinal lesion produced by the Toxoplasma is represented ophthalmoscopically by localized edema with indefinite peripheral demarcation and early necrosis in the central part of the lesion. The retinal vessels are normal. Later, the central part of the lesion becomes definitely atrophic so that the sclera becomes visible. Pigment clumps appear at the border of the central atrophic area and pigment in more granular distribution in and at the margin of the edematous peripheral zone. Still later the lesion loses the appearance of edema, becomes sharply marginated, and may show atrophic and depressed zones,

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or else elevated, avascular, homogeneous fibrous masses with possible invasion of granulation tissue into the vitreous. The entirely healed and inactive lesions appear as "sharply marginated areas of chorioretinal atrophy or proliferation, of varying degree, with diffuse irregular pigment deposition, more concentrated at the margins. The retinal vasculature remained surprisingly normal."

Koch and his co-authors think that toxoplasmic chorioretinitis occurring in infants and young children must be differentiated from pseudoglioma, intra-ocular tumors, especially retinoblastoma, traumatic lesions (birth injuries), hereditary cerebromacular degeneration, congenital developmental defects, tuberous sclerosis, acute metastatic chorioretinitis in upper respiratory infections, acute exanthems, malaria and the like, tuberculous or other forms of meningitis, and syphilitic, tuberculous and leprous granulomas. They present as characteristic features of toxoplasmic chorioretinitis: "(1) occurrence of severe and extensive focal chorioretinal lesions in infants and children; (2) regularity of bilateral involvement of the macular region; (3) tendency to bilateral occurrence of other lesions; (4) tendency to involvement of the periphery in one or more quadrants of the retina and choroid; (5) punched-out appearance of large and small lesions in the late phase; (6) occurrence of massive chorioretinal degeneration, extensive connective tissue proliferation and heavy pigmentation, as contrasted with the dissociation of these changes in other chorioretinal lesions; (7) presence of an essentially normal retina and vasculature surrounding the lesions in all stages of the infection; (8) tendency to the occurrence of associated congenital defects in the eyes; (9) rapid development of sequential optic nerve atrophy; and (10) constant clarity of the media in the presence of severe chorioretinitis (with one exception, the left eye in Case 4)." They think that the other clinical signs and symptoms present in the case are helpful in the diagnosis when the ophthalmoscopic findings are not clearly diagnostic. "Symptoms and signs beginning at birth or early in life, a subacute or chronic course, evidence of widespread involvement of the nervous system, convulsive seizures, internal hydrocephalus, and the occurrence of intracerebral calcification all point to the presence of infantile toxoplasmic encephalomyelitis, of which toxoplasmic chorioretinitis is an outstanding feature. Antitoxoplasmic activity of the serum tends to confirm this diagnosis." They state further: "It would appear that toxoplasmic chorioretinitis occurs in most, if not in all, instances of infantile toxoplasmic encephalomyelitis and is of diagnostic aid in the clinical recognition of this disease. It should be regularly sought in infants and children with a history of convulsions, hydrocephalus, mental retardation, speech difficulties, defective vision, or intracerebral calcification first observed in early infancy."

The occurrence of toxoplasmic chorioretinitis and encephalomyelitis in twin infants was reported by Heath[3] at the recent meeting of the American Ophthalmological Society. The details of these cases are not available for presentation here, since they have not been published as yet. Heath seems to believe, along with Koch, that the chorioretinal lesions in these cases are always bilateral, are essentially always multiple, essentially always involve the maculas, and that they are most frequently associated with congenital anomalies of the eyes. It may be of interest that I have observed recently a single unilateral healed and atrophic chorioretinal lesion which did not involve the macula, in an infant with congenital hydrocephalus and multiple small areas of intracerebral calcification in the roentgenograms of the head. The blood serum of this infant possessed

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neutralizing antibodies to Toxoplasma. The eyes appeared to be otherwise normal.

In 1943, Vail, Strong and Stephenson[16] reported 6 patients with chorioretinitis in whom the lesions were apparently associated with Toxoplasma infection. Four of the patients were children, aged 7, 7, 7 and 12 years, at the time of the first discovery of the choroiditis. One patient was 16 years of age and the other 23. Neutralizing bodies against Toxoplasma were found in the blood sera of both the patient and the mother in all 4 of the children and the authors considered the disease to be of congenital origin in 1 other case also. They believed that, in the 6th case, it had been acquired in later life. In 3 of the cases the lesions were healed and inactive. In 3 the lesions were progressive though, at the time of the first examination, they appeared to be inactive. Three patients showed unilateral and 3 bilateral involvement. In 1 patient, at the first examination, a diagnosis was made of bilateral central chorioretinitis and bilateral secondary optic atrophy of congenital origin. The lesions in the maculas were apparently healed and showed no change during an observation period of 4 years. One year later the chorioretinitis had been disseminated throughout the left eye. Two years after this an acute anterior and posterior uveitis developed in the left eye, subsided in about 1 month, recurred 4 months later, and again subsided in about 6 weeks. At this time, the chorioretinitis was observed to be disseminated in each eye with recurrent active foci. In the 2 other patients in whom there was evidence of active inflammation, the lesions were unilateral; in 1 single and involving the macula, in the other multiple but not involving the macula. Of the 3 inactive lesions, 1 was unilateral and involved the macula; the other 2 were bilateral and disseminated with involvement of the macula. Evidence of cerebral calcification was found in only 1 of the cases. Two of the patients had convergent strabismus. No mention is made of any other congenital anomaly of the eyes.

In general summary of the eye lesions which they had observed, Vail, Strong and Stephenson[16] state: "The fundus usually reveals a chorioretinitic lesion, unilateral or bilateral, having a predilection for the macular area. It has a grayish white center, is irregular, bordered with dark pigment, and surrounded on one or more sides by faint choroidal hemorrhage. The spread of the lesion is usually in the direction of the hemorrhage. The lesion may be elevated. Iridocyclitis, vitreous opacities, retinitis proliferans, and detachment of the retina may result. Central vision is always adversely affected." In this statement, the authors evidently have reference to some characteristics of the acute or active lesions which, in their opinion, may be of etiologic diagnostic significance. They state with reference to the inactive lesions that "nothing characteristic was found in the fundi that could classify them as typical of Toxoplasma." They believe that infection with Toxoplasma may be more prevalent among the general population than has been generally supposed and that in any obscure pathologic condition of the eye, tests for the presence of Toxoplasma neutralizing antibodies are indicated. They conclude that "many cases of chorioretinitis formerly diagnosed as tubercular, metastatic, or of unknown etiology may be due to Toxoplasma, especially if associated with cerebral calcification."

Also in 1943, Lichtstein and Solis-Cohen[10] reported 2 cases of familial epilepsy under the diagnosis of familial tuberous sclerosis. The father, aged 46, had had 2 epileptic seizures during a 12-year period. Roentgenograms of the skull revealed 2 small calcifications in the region of the left

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lateral ventricle. The eyegrounds were normal. The son, aged 22, had had epileptic attacks since the age of 2 and showed some evidences of mental deterioration. Roentgenograms of the skull showed a number of small, irregularly calcified deposits, probably within the ventricles. Vision was poor. Ophthalmoscopic examination revealed extensive choroidal changes with large areas of atrophy in the maculas and moderately advanced optic atrophy. The eyes were highly myopic. "The lesions were believed by the ophthalmologist to be on the basis of a hereditary macular degenerative process, congenital and colobomatous in origin." Merritt and Aring[11] and also Koch[7] expressed the opinion that these were really cases of toxoplasmic encephalomyelitis. In his comment, Koch states: "Typical retinal tumors, not unlike the surface of an unripe mulberry in appearance, invariably occur in tuberous sclerosis, while in congenital or infantile toxoplasmic encephalomyelitis there are seen essentially without exception bilateral, more or less atrophic as well as pigmented, central (or macular) as well as more peripheral, fairly extensive patches of chorioretinitis. It is most probable that the onset of these patches in their acute phases occurs prenatally or in infancy or in both but not in childhood or later. There is no reason, however, to suppose that they do not continue to exist throughout the life of the afflicted patient or that they do not remain diagnostically recognizable. The latter is equally true with regard to the characteristic tumors of the optic disk and of the retina in tuberous sclerosis, an entity in which chorioretinitis has not yet been observed as such, probably for the very good reason that the tumors are not inflammatory or microörganistic in origin."

There would seem to be no better way to summarize the situation with regard to toxoplasmic chorioretinitis as it appears to stand today than by some quotations from a recent article by Vail. "Cases of disseminated and circumscribed exudative chorioretinitis are relatively common." "The etiology of chorioretinitis, however, presents many problems and in far too many cases the cause perforce remains obscure. It is for this reason that evidence which indicates that a parasite which is probably not rare produces choroiditis in some cases assumes importance and warrants discussion, even if the evidence may not be quite complete." "The ophthalmologic findings in both the infantile and adult cases are the familiar ones of circumscribed exudative choroiditis. There is a predilection for the macular area and the lesions are usually bilateral and multiple." "In 11 of the cases described the condition was probably congenital, in the 12th it was without doubt acquired. Three additional cases occurring in adults past the third decade under my observation have not yet been reported. These are probably acquired cases of toxoplasma." Vail points out that, although Koch and his associates think that there are some ophthalmoscopic diagnostic features of toxoplasmic chorioretinitis, he has not been able to make the diagnosis from the ophthalmoscopic appearance alone in the older children and adults he has seen. The diagnosis depended on the demonstration of Toxoplasma neutralizing antibodies in the blood serum. Vail[17] thinks that more studies are needed to prove the validity of this neutralization test. The test as at present performed seems to be of considerable difficulty. Perhaps more cases would be discovered if a more universally applicable and, at the same time, reliable laboratory test was devised. Sabin[14] spoke in 1941 of the possibility of a complement-fixation test of which Warren[18] and he stated in 1942, "While a positive complement-fixation reaction does not in all cases indicate active or even recent infection, it is believed that this test may

have its greatest usefulness in the rapid diagnosis of active toxoplasmosis." There seems to be no very satisfactory treatment for this disease, though various forms of sulfonamides have been tried.

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BOOK REVIEWS AND NOTICES

AMERICAN MEN OF SCIENCE. A Biographical Directory. Edited by JACQUES CATTELL. Seventh ed. Pp. 2003. Lancaster, Pa.: The Science Press, 1944. Price, $14.00.

THIS well-known and invaluable book of reference requires no explanation or recommendation to American scientists. We agree with the Editor that the advantage of having an enlarged revised edition at this time outweighs the disadvantages associated with war-time production; and that, if only from the point of view of saving scientists' time and energy, it is a contribution to the war effort. The new edition contains about 34,000 names, as compared with 4000 in the first edition, and 28,000 in the sixth. "A selection has again been made by their colleagues of the 250 total additional selections for this edition(?) who in the course of 5 years have attained a position among our leading scientific workers . . . . by the same methods as those used in previous editions." This presumably refers to the asterisks appearing before the name of each individual's specialty. In the case of certain individuals, the small number following the asterisk indicates the edition in which it first appears. Possible modifications of this procedure were not put into effect, as the A. A. A. S. Committee appointed to study the subject has been prevented from functioning by the war.

We recommend the volume highly to all those engaged in scientific work.

E. K.

SYNOPSIS OF OBSTETRICS. By JENNINGS C. LITZENBERG, B.Sc., M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, Univ. of Minnesota Medical School, Minneapolis. Second ed. Pp. 405; 157 illus. (5 in color). St. Louis: C. V. Mosby, 1943. Price, $5.00.

THIS book gives a very concise and complete review of obstetrics. It is well written, very clear, and contains many valuable illustrations. It makes an excellent teaching manual. I recommend it highly for a quick review of obstetrics.

H. F.

CIVILIZATION AND DISEASE. By HENRY E. SIGERIST, M.D., D.LITT., LL.D., William H. Welch Professor of the History of Medicine in Johns Hopkins University. Pp. 255; 52 figs. Ithaca, N. Y.: Cornell Univ. Press, 1943. Price, $3.75.

THE 12 chapters of this latest production of a prolific pen are expanded from the 6 Messenger Lectures given at Cornell by Dr. Sigerist in 1940. They consider the relationships between disease and such facets of civilization as economics, the law, social life, history, religion, philosophy, science, literature, art, music. The opening and longest chapter, Civilization as a Factor in the Genesis of Disease, discusses the rôles of nutrition, of costume and personal hygiene, of housing and sanitation in the production of disease. This is well-balanced by a final chapter on civilization's progress in the struggle against disease.

The treatment of the subject matter is from the historical point of view, aimed at the layman, and necessarily fragmentary, presumably because of space considerations. However, the Author quickens our interest by the insertion of many critical and illuminating comments, which rise in powerful crescendo through the last few pages. It may be a cliché to say that in this country the technology of medicine has out-run its sociology—but this detracts

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not at all from the value of Sigerist's emphasis on the need for cutting down the number of unnecessary and premature deaths and lost working days. Furthermore, no one can properly object to the position he takes that poverty, ignorance and medical ineffectiveness are the chief factors in lowering health conditions. Dr. Sigerist's years of careful study of Soviet medicine and health maintenance, which have made him easily the best informed authority on this subject in the United States, have led him to what many authorities regard as too radical a stand on these matters as applied to America. But this aspect he leaves largely untouched in this book; and surely we may all agree with him that standards of living and of education and health conditions must be raised as high as possible throughout the world. True is it also that "a new medicine serving a new society requires new forms of service." But what is a reasonable interpretation of "as high as possible" and what should these new forms of service be? There's the rub! The Reviewer humbly acknowledges that he neither practices medicine nor concerns himself closely with the very necessary activities of organized medicine. Even so, however, it seems almost inevitable that the American temperament, and our economical and educational standards and medical efficiency being what they are, the introduction of sweeping and revolutionary governmental control and centralization of power in the hands of a single federal official would shortly replace our sound evolutionary progress toward new forms of medical service (slow though it may be), with a degradation of medical efficiency that would far outweigh any advantages gained. E. K.

THE MEDICAL CLINICS OF NORTH AMERICA. Chicago Number. Symposium on Cardiovascular Diseases. Pp. 289; 37 figs.; 7 tables. Philadelphia: Saunders. Price, $16.00 per year.

THE January 1944 number of the Medical Clinics of North America contains 2 interesting symposia. The first deals concisely, yet adequately, with several broad problems of cardiovascular diseases in the usual direct manner of the "Clinics." Diseases of the blood-forming organs constitute the theme of the second symposium, with emphasis placed on the increasingly important subject of the Rh factor in 2 of the 7 articles of this group.

An isolated article on the treatment of Pneumonia with Sulfadiazine, and another reëmphasizing the ever-present errors in diagnosis of neoplastic lesions of the large bowel conclude this number from Chicago. R. M.

PANCREATIC FUNCTION AND PANCREATIC DISEASE STUDIED BY MEANS OF SECRETIN. By HENRIK O. LAGERLOF, M.D. Translated by HELEN D. DREY. Foreword by JOSEPH H. PRATT, M.D. Pp. 289; 50 tables. Printed in Sweden. New York: Macmillan, 1942. Price, $3.50.

THIS book deals primarily with the technique, results and interpretation of the secretin test for pancreatic function. At the same time the physiology and the clinical disturbances of the pancreas are presented under these chapter headings: normal external pancreatic secretion, acute pancreatic disease and chronic pancreatitis, the secretin test, general discussion and case reports.

The procedures for the determination of the bicarbonate, amylase, trypsin and lipase content of pancreatic juice are amply and clearly outlined. Factors that may influence results are also emphasized. For practical purposes, the book stresses the value of the bicarbonate and amylase determinations alone as sufficing to indicate the functional or pathologic state of the pancreas.

One strong feature of the text is the emphasis on the statistical treatment of the figures obtained. Thus, one gets the impression that the final figures and the conclusion derived therefrom are much more reliable than are the customary average medical quantitative reports.

Some space is devoted to the clinical aspects of pancreatic disease. The case reports, with their operative or autopsy findings, attempt to correlate the laboratory tests with the strictly clinical picture.

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By way of recommendation, one may state that the physiologic action of the Swedish preparation of secretin (which is the basis of the studies in the book) and its diagnostic value have been demonstrated and confirmed in this country by such students of pancreatic function and disease as Diamond, Comfort and Pratt.

The book will be useful to the gastro-enterologist and to any physician interested in hepato-biliary-pancreatic disorders. G. A.

TEXTBOOK OF GYNECOLOGY. By EMIL NOVAK, M.D., F.A.C.S., Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore. Second ed. Pp. 708; 456 figs. Baltimore: Williams & Wilkins, 1944. Price, $8.00.

THE first edition of Novak's text appeared in 1941 under the title Gynecology and Female Endocrinology. The present volume has been expanded by nearly 100 pages. A chapter has been contributed on the common disorders of the female urinary organs by Houston S. Everett. The volume is written primarily for the student and general practitioner. One of its chief values lies in the large number of beautiful illustrations, many of which are produced in color. Its chapters on female endocrinology give the reader an excellent review of the problems which sometimes are brought to the gynecologist who is interested in this branch of his subject. This volume is to be highly recommended as a classroom text. D. M.

RECENT ADVANCES IN MEDICINE. By G. E. BEAUMONT, M.A., D.M. (OXON.), F.R.C.P., D.P.H. (LOND.); Physician to the Middlesex Hospital, Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School; and E. C. DODDS, M.V.O., D.Sc., PH.D., M.D., F.R.C.P., F.I.C., F.R.S. (EDIN.), F.R.S., Courtauld Professor of Biochemistry in the University of London (Middlesex Hospital). Eleventh ed. Pp. 412; 43 figs.; many tables. Philadelphia: Blakiston, 1943. Price, $5.50.

THE 11th edition of this small handbook suggests that it fills a definite need for both practicing physician and student alike. The book reflects the British point of view and differs in some respects from the American teachings. For example, the evaluation of the sulfonamide drugs now in use does not seem to be supported by the American literature on this subject. The discussion of electrocardiography fails to emphasize significantly the importance of chest leads; and, in fact, the authors still speak of only one chest lead.

Although there are points of value in this monograph it seems to the Reviewer that better material is available elsewhere. F. M.

OLD AGE IN NEW YORK CITY. An Analysis of Some Problems of the Aged, Based on 3106 Requests for Information About Health and Welfare Services. By HELEN HARDY BRUNOT. Pp. 128; many tables. New York: Welfare Council of New York City, 1944. Price, $1.50.

A USEFUL and highly commendatory attempt to solve some of the problems of aging, which have aroused much interest during the last few years, has been the creation of a Bureau for the Aged by the Welfare Council of New York City. This group has now brought out a study of old age in that city. Under the direction of this Bureau, the important factors that make up the problem of aged people have been classified and critically examined.

The inquiry upon which this report is based is extended over a 2½ year period, during which 3106 requests for information were received. These requests were carefully investigated and evaluated in order to show the type of personal problems that were being faced by the old people of New York

and their experiences with the available community agencies to which they turned for assistance.

The body of the report is divided into 5 sections. After dealing with the function of the Bureau, the sources of material and the methods of investigation, sections follow which take up the age and sex distribution of the group studied and their social and economic backgrounds, the problems of physical and mental health in old age, the question of support in old age, and, finally, social relationships and environment as applied to the aged.

One result of this study has been to confirm the dictum, "That old age itself does not constitute a social problem since it is natural and inevitable but that the conditions which surround the aged, including the attitude of younger people, create the problem." The report is a well-prepared, clearly stated and thoughtful document. It is based upon a painstaking, scientifically conducted investigation in which the investigators approached their problems not only intelligently but with a sympathetic understanding. The report can be studied with profit by all agencies and all individuals who are concerned with the welfare of older people. Until social agencies, the general public, and particularly families and friends of older people, are firmly impressed with the fact that, "the first requisite to a more intelligent and humane community program for services aimed to benefit aged persons is a recognition of their individuality as persons," no program can serve effectively the needs of the ever-increasing number of older individuals, not only in New York City but in all of our communities. G. P.

THE JEWS AND MEDICINE ESSAYS. By HARRY FRIEDENWALD, M.D., D.H.L. (HON.), D.Sc. (HON.), Professor Emeritus of Ophthalmology, University of Maryland. Preface by HENRY E. SIGERIST. Publications of the Institute of the History of Medicine, The Johns Hopkins University. First Series: Monographs. Volumes 2 and 3. Pp. 817; many figs. Baltimore: The Johns Hopkins Press, 1944. Price, $3.75 per volume.

BUT a brief perusal of these essays is required to demonstrate the author's protracted and productive interest in Jewish culture and in the contributions of Jewish physicians to the progress of medicine. These volumes, which constitute the 2nd and 3rd volumes of the Monograph Series of Publications of the Institute of the History of Medicine, are composed of 42 articles mostly reprinted from, or in a few cases based on, previously published articles. They range over many years, from 1917 to the 1940s, and over a wide field—Jewish booklovers, practitioners and the practice of medicine, Jews and the Universities, hospitals, diseases of the Jews, and so on. Two monographs of more ambitious scope, listed as Chronicles, are on Jewish Physicians in Italy: Their Relation to the Papal and Italian States (63 pp.) and History of the Jewish Physicians of Spain, Portugal and Southeastern France (160 pp.). Though, for the most part, such Chronicles are drier reading than the warmer, biographic sketches, topical essays, and *obiter dicta*, they too have their proper place in a medical historical library, as valuable works of references.

The medical profession owes much to the Friedenwalds of Baltimore and not the smallest of our debt is that brought about by the publication of these 2 interesting and scholarly volumes. E. K.

THE PRINCIPLES AND PRACTICE OF MEDICINE. Originally written by SIR WILLIAM OSLER, BART., M.D., F.R.C.P., F.R.S. Designed for the use of practitioners and students of medicine by HENRY A. CHRISTIAN, A.M., M.D., LL.D. (HON.), Sc.D., (HON.) F.R.C.P. (CANAD.), F.A.C.P. Fifteenth ed. Pp. 1498. New York: D. Appleton-Century, 1944. Price, $9.50.

A NEW edition of "Osler" is always something to look forward to; it is especially satisfying to see this hardy perennial continuing to appear at such

frequent intervals—this being the 6th edition to be published in the past decade. It is also notable, in these days of multiple authorship, that a single author can keep a work of this size and scope so well abreast of the rapidly changing times.

As Dr. Christian, in his Preface, expresses pleasure in his contact with those voicing suggestions, and regrets that anonymous reviews prevent his pursuing the Reviewer's remarks farther (though doubtless the Editor would supply the Reviewer's name and address on request), the present Reviewer started notes as to suggested changes and modifications. As these, in print, however, could not avoid creating an erroneous atmosphere of adverse criticism where none was intended, and doubtless at times would contain no germ of improvement, the suggestions have been confined to private correspondence. For the book as a whole, there can only be praise.

Conforming to the policy started in the 14th (semi-centennial) edition, this edition has been ". . . . so organized that important new material will be quickly incorporated, so that there will be in the future not occasional but frequent new editions of the text," and medical progress with its accelerated tempo thereby better presented. The slight handicap of rare blank or partly filled pages, with accessory numbering of pages (such as "72(1)"), is a small price for a reader to pay for the greater advantage mentioned. In fact, this may easily prove to be at least a partial answer to the loose leaf system as applied to medicine, with its tedious requirements of frequent shifting of old and new leaves.

As before, the text begins with functional nervous diseases and ends with organic nervous diseases, an unusual schism of doubtful advantage. Infections and parasitic diseases, intoxications and so on occupy almost half the book, the rest being taken up by diseases of the digestive and other systems. Due regard has been paid to the special needs raised by war conditions: the many tropical and venereal diseases, the increased chances of occurrence of various epidemics, the rise of new and potent drugs, the increased need for the newest and best methods of diagnosis, prophylaxis and treatment—"all of this will be found in this edition in a very complete and up to date fashion" (Preface). The dates of the articles included in the references at the end of each section amply confirm the up-to-datedness of this excellent book.

E. K.

OFFICE TREATMENT OF THE NOSE, THROAT AND EAR. By A. R. HOLLANDER, Associate Professor of Otolaryngology, Univ. of Illinois. Pp. 480; well illustrated. Chicago: Year Book Publishers, 1943. Price, $5.00.

THIS book should be in the hands of all who treat conditions of the upper respiratory tract. All modern concepts of treatment are prescribed. The bibliography is excellent. The Reviewer gives unreserved recommendations.

K. H.

EVOLUCION Y FUNCION BIOLOGICA DE LAS PROTEINAS. By JULIO MENDEZ, Physician of the J. M. Ramos Mejia Hospital; Honorary Professor of the School of Medicine of Buenos Aires, Cordoba, and La Plata. Pp. 139. Buenos Aires: Guillermo Kraft, 1943.

THIS book consists of 6 lectures given by the author at the School of Medicine of the Universidad Nacional of Buenos Aires on the evolution and biologic functions of the proteins. The exposition is very clear and the style is eloquent and precise. He discusses the chemical structure of proteins and subdivides them into macroproteins (fibrinogen, fibrin, collagen), mesoproteins (euglobulins, pseudoglobulins), and microproteins (serum albumins, amino acids). It is a debatable question whether or not this classification tends to clarify the study of this group of compounds.

The name "lysins Mendez" is given to the amino acids in the body, and the rôle of these compounds as active agents in pathologic conditions is presented

as a theory of the author. Furthermore, some of the expressed concepts of allergy, anaphylaxis and immunity do not agree with the prevalent ideas. Water balance, edema, nephrosis, acidosis, alkalosis, inflammation, and so forth, are discussed.

The book provides interesting information regarding the author's point of view on some physiologic processes, though they may not be entirely in agreement with the current theories on the subject. L. G.

A MANUAL OF MEDICAL PARASITOLOGY. By CLAY G. HUFF, Professor of Parasitology, Univ. of Chicago. Pp. 88; 10 plates. Chicago: Univ. of Chicago Press, 1943. Price, $1.50.

PARASITOLOGISTS have complained for some time that their subject has not received adequate recognition in the curricula of medical schools in this country. Now that current circumstances have emphasized the importance of parasitic diseases and more time is being allotted to their study, one may wonder that there has been this neglect. Perhaps it has reflected the isolationist attitude of the nation, perhaps it has been a result of overcrowded curricula, or possibly it was related to the manner in which the subject had been presented.

This manual is an outgrowth of notes used for the past several years in the course in Medical Parasitology at the Univ. of Chicago. General arrangement of the text is shown by the following chapter headings: 1. Trematodes or Flukes; 2. Cestodes or Tapeworms; 3. Nematodes or Roundworms; 4. Intestinal Protozoa; 5. Hemoflagellates; 6. Malarial Parasites of Man; 7. Mosquitoes Which Transmit Disease; 8. Flies Which Transmit or Cause Disease; 9. Other Bloodsucking Insects Which Transmit Disease; 10. Ticks and Mites —Order Acarina; 11. Laboratory Diagnosis of Parasitic Infections.

The book is illustrated by 1 composite chart of trematode life histories (which is too complex for teaching purposes) and by several other simpler and more useful figures. The colored plate of 3 species of Plasmodium of man is especially good. In part the text is a conventional discussion, interspersed here and there with more or less extensive and detailed directions for laboratory exercises to which questions are appended.

This arrangement of the material brings the student into contact with uncommon parasites first, and laboratory exercises suggest study of details of morphology of parasites of man or of organisms from other hosts, which, while important to a student of parasitology as such, have no part in an understanding of parasitic disease, their diagnosis and control. Instruction in Parasitology in medical schools would accomplish its rightful aims if the students understood how animal parasites cause disease and how infections may be recognized and controlled. There is certainly not time for more extended considerations. When parasitologists come to understand that and present the subject accordingly, perhaps it will receive the attention it deserves. Professor Huff's manual is not a means to this end. H. R.

MAURICE ARTHUS' PHILOSOPHY OF SCIENTIFIC INVESTIGATION. Preface to De l'Anaphylaxie à l'Immunité, Paris, 1921. Translated from the French, with an Introduction by HENRY E. SIGERIST. Foreword by WARFIELD T. LONGCOPE. (Reprinted from Bulletin of the History of Medicine, Volume XIV, No. 3, October, 1943, pp. 366–390.) Pp. 26. Baltimore: Johns Hopkins Press, 1943. Price, $.75.

THE distinguished French physiologist, for whom the "Arthus phenomenom" is named, wrote a chapter of advice for those beginning a career of experimental physiology. In this preface he warns students against the "theoreticians" and extols the scientific method. The experimentalist is urged to seek the answer to only one question at a time, having formed the question in such a way that it may be answered by yes or no.

Dr. Sigerist has furnished an admirable translation. M. M.

MANOMETRIC METHODS as Applied to the Measurement of Cell Respiration and Other Processes. By MALCOLM DIXON, PH.D., SC.D., F.R.S., Univ. Lecturer in Biochemistry in the Univ. of Cambridge. Foreword by SIR F. G. HOPKINS, O.M., F.R.S. Second ed. Pp. 155; 20 figs.; 6 tables. Cambridge: Univ. Press; New York: Macmillan. Price, $1.75.

THE study of the metabolism of isolated surviving tissues *in vitro* has extended into many biologic and medical fields. Since the original development by Warburg, manometric methods for the determination of the gas exchange of such tissue have increased in number, complexity and refinement. Dixon's able book has always been a standard in this field and a new edition is welcomed by technologists in the field. The text has been thoroughly revised, and new sections have been added, *viz.*, measurements in serum, micro methods, and so forth. The bibliography has also been brought up to date. W. S.

MEDICINE AND THE WAR. Edited by WILLIAM H. TALIAFERRO. Foreword by WILLIAM T. HUTCHINSON, Executive Secretary, Charles R. Walgreen Foundation for the Study of American Institutions. Pp. 193; several figs. and tables. Chicago: Univ. of Chicago Press. Price, $2.00.

WAR always reëmphasizes human problems; economic, social, political, philosophic, ethical. Medicine also presents many aspects which in peace time are hazy and ill-defined, but which now require sharper delineation. This small volume contains a series of lectures given under the auspices of the Walgreen Foundation by a group from the University of Chicago Medical Faculty. It sums up in brief, clear and entertaining style most of the current war problems of medicine. The chapters which are particularly informative are those devoted to Chemotherapy; Malaria; Insects, Disease and Modern Transportation; and Shock and Blood Substitutes. Among other topics of general interest are: Food and the War; Aviation Medicine; Neurological and Psychological Effects of Cerebral Injuries; Psychiatry and the War; and Chemical Warfare.

The book is recommended reading to those who wish to obtain quickly a speaking acquaintance with recent progress and trends in these various aspects of war medicine. W. S.

MEDICAL CARE OF THE DISCHARGED HOSPITAL PATIENT. By FRODE JENSEN, M.D., Instructor in Medicine, Syracuse Univ. College of Medicine; H. G. WEISKOTTEN, M.D., Dean and Professor of Pathology, Syracuse Univ. College of Medicine; and MARGARET A. THOMAS, M.A. (OXON.). Pp. 94; 4 tables. New York: The Commonwealth Fund, 1944. Price, $1.00.

THE University Hospital of Syracuse, N. Y., through its activity in teaching domiciliary medicine to medical students, became increasingly aware of the unsatisfactory nature of medical care for most of its ward patients after discharge from the Hospital. This book is a report of their experiment in extending medical supervision beyond the limits of the Hospital walls. Figures are presented showing that the extension of medical care shortened hospital stay and prevented readmission.

An instructor in Medicine was appointed as Extra Mural Resident, and he was assisted by a lay Social Investigator. All patients (902) discharged from the medical wards for a period of 18 months came within the scope of the project. The Extra Mural Resident discussed with them all their plans for care after discharge. He acted as family physician for the patients needing home care and having no private physician, and as a coördinator of medical care for those who could be served by the Dispensary; those who returned to the care of private physicians; and those who were discharged to institutional care. Since 84% of the total group were chronically ill, the emphasis of the report is on medical and social problems of this group.

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If hospitals are going to become more concerned in preventive medicine and in patients beyond the acute stage of illness, this report is interesting as an indication of one method of approach to the problem. The method reported may not be the solution, or might require considerable modification to be practical, but it certainly is aimed at the solution of one of medicine's most besetting problems, *i. e.*, how to prevent waste of medical care. Anyone interested in this subject will find the bibliography of great value. M. P.

SAFE CONVOY. The Expectant Mother's Handbook. By WILLIAM J. CARRINGTON, M.D., A.B., F.A.C.S., Attending Gynecologist, Atlantic City Hospital, Atlantic County Hospital for Nervous and Mental Diseases, Pine Rest Hospital, Atlantic City Municipal Hospital and Atlantic Shores Hospital; Diplomate American Board of Obstetrics and Gynecology; Former Vice-President, American Medical Association. Pp. 253. Philadelphia, New York: J. B. Lippincott Company, 1944. Price, $2.50.

THIS volume of 256 pages is a comprehensive consideration of the reproductive process which has been written for the expectant mother. The author writes in an entertaining manner and covers his subject well. He has deemed it necessary to include a glossary of some 350 terms. This fact leads the Reviewer to wonder whether the average expectant mother will be able to digest its contents with ease. With that one exception the volume is without adverse criticism. D. M.

THE CARE AND FEEDING OF CHILDREN. Revised and Enlarged by L. EMMETT HOLT, JR., M.D., Associate Professor of Pediatrics, Johns Hopkins Univ.; Associate Pediatrician, Johns Hopkins Hospital, Baltimore, Md. Sixteenth ed. Pp. 321; illustrated. New York and London: D. Appleton-Century, 1943. Price, $2.00.

THIS latest revision of one of the oldest and most popular baby-raising guides contains new material on "simplified milk formulas, up-to-date food and vitamin data, information on allergy and inoculations, and a section on behavior problems, to mention a few" (quotation from the jacket). Its contents are organized under the following chief headings: Care of Infants, Growth and Development of Infants, Breast Feeding, Artificial Feeding, Feeble and Premature Infants, Older Children, Behavior Problems, and Common Ailments of Childhood. The discussions, arranged in short question-and answer form, are couched usually in broad terms.

The curious mother of a baby or growing child will find in this book satisfying information regarding the common problems which come up while rearing a young citizen from cradle to adolescence. Though not every pediatrician would agree with every statement made, the textual advice conforms in general with the point of view of contemporary pediatric practice. I. W.

LABORATORY METHODS OF THE UNITED STATES ARMY. Edited by JAMES STEVENS SIMMONS, B.S., M.D., PH.D., D.P.H., SC.D.(HON.); and CLEON J. GENTZKOW, M.D., PH.D. Fifth ed. Pp. 823; 108 tables; 103 figs. (8 color plates). Philadelphia: Lea & Febiger, 1944. Price, $7.50.

THIS edition, like the first, prepared to meet the current war time needs, is now, as one might readily imagine, considerably larger than its predecessor. Yet by the military conciseness of presentation that it possesses, a wide range of subject matter is kept within the limits of an easily manageable volume—no mean advantage for the many "huts" and "tents" to which this book will penetrate. Its 11 parts, none without great practical value, cover a considerably wider range than the usual work of laboratory diagnosis: Clinical Pathology, Chemistry, Mycology, Bacteriology, Rickettsiæ and Filtrable Viruses, Protozoölogy, Helminthology, Medical Entomology, Pathology, Special Veterinary Methods, Statistical Methods of the more important sections.

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Part I, so-called "Clinical Pathology," though including Pregnancy Tests, Blood Groups and Transfusions, and the Serodiagnosis of Syphilis, is considerably shorter (126 pages) than Part II on Chemistry (220 pages) and Part IV on Bacteriology (178 pages). The last Part, on Statistical Methods, by General P. R. Hawley, Chief Surgeon in the European Field of Operations, is a novel and desirable feature in a book of this kind. One approaches it hopefully as "designed for the laboratory worker, interested in fields other than mathematics." This tactfully expressed aim, however, has not produced a handy statement for the beginning user of statistical methods. The very condensed style in itself, makes it as difficult, or perhaps even more difficult, to follow than larger treatments of the subject.

Of the 25 contributors about one-half are from civilian life, and a good third are notable authorities. One may indeed wonder how such an excellent up-to-date job has been accomplished by men all of whom must be carrying heavy loads of routine. They have produced a first class handbook with the needs of the military kept to the fore, but one that is just as useful in civilian laboratories and to veterinarians and public health workers. E. K.

A Manual of Physical Therapy. Formerly published under the title "Physical Therapy for Nurses." By Richard Kovacs, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus, and West Side Hospitals New York. Third ed. Pp. 309; 29 tables; 118 figs. Philadelphia: Lea & Febiger, 1944. Price, $3.25.

In this revised edition the author has presented a brief, concise compendium of physical therapy, especially as it applies to the increasingly important rôle it is now assuming in the treatment of war injuries. The introduction gives the reader a picture of the scope, basis and history of physical therapy. Then the author presents an excellent discussion of the physics, physiologic effects, and the therapeutic application of heat, artificial fever, natural and artificial ultraviolet radiation, electrotherapy (including low frequency currents, long and short wave diathermy, static electricity, and electrodiagnosis), hydrotherapy, massage and exercise. There is included in the book a chapter by Dr. Madge C. L. McGuinness, who gives a comprehensive development of the physiology, classification and description of general and special exercises as they apply in the general practice of physical therapy; and as developed in the Army Reconditioning Program. There also is a chapter with suggestions and diagrams covering all the important points in the organization and conduct of a physical therapy department for institutional practice. The book is compact, clear, and concise, with an excellent organization of the subject by chapters. There are also review questions at the end of Parts 2, 3, 4 and 5 that add to the teaching value of the book.

It is the opinion of the Reviewer that the author has given to the field of physical therapy a brief, practical reference that will be a valuable addition to any library. W. T.

Small Community Hospitals. By Henry J. Southmayd, Director, Division of Rural Hospitals, The Commonwealth Fund; and Geddes Smith, Associate, The Commonwealth Fund. Foreword by Barry C. Smith, General Director, The Commonwealth Fund. Pp. 182. New York: The Commonwealth Fund, 1944. Price, $2.00.

This book brings to the public the accumulated experiences of the Commonwealth Fund in their program to improve the quality of medical care in the smaller communities of this country. It should become the handbook of any group of citizens interested in this fundamental and vital problem. While written primarily for the layman, its detailed discussion of plans, organization, and procedures will be of inestimable value to physicians and administrators interested in the improvement of hospital and medical care in rural communities. R. B.

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ORAL HISTOLOGY AND EMBRYOLOGY. Edited by BALINT ORBAN, M.D., D.D.S. Pp. 342; 262 illus., 4 color plates. St. Louis: C. V. Mosby, 1944.

THE rapid advance in knowledge of the oral tissues over the last decade has materially changed our histologic insight. Thereby also new light is spread on pathologic processes. Investigators in the histologic field often disagree as to findings and interpretations. This difficulty is overcome by proper planning of the book. Prominent men in the field of oral histology were requested to write outlines on different detail which they had personally investigated. The outlines were subsequently discussed and criticized by these men collectively. The different viewpoints were coördinated by the editor, embodied in chapters which were often redrafted and finally approved in essential by all contributors. Likewise the resources of all collaborators were pooled and the best illustrations of their material selected.

The student of oral histology is finally given a textbook in which confusion resulting from differences in opinion is avoided. Clinical applications are added to each chapter. The result is a textbook which is a real contribution to the practice of dentistry. We believe that the arrangement of the chapters could be improved upon. Thus Chapter I on the Development of the Face and Oral Cavity could have been followed by Chapter VIII Concerning the Maxilla and Mandible, Chapter XV on The Maxillary Sinuses, Chapter XIV on The Temporomandibular Joint, Chapter XII on Oral Mucous Membrane and Chapter XIII on Glands of the Oral Cavity. Chapter II dealing with the Development and Growth of Teeth is properly followed by Chapters III to VII on Enamel, Dentin, Pulp, Cementum and Periodontal Membrane, after which could have followed Chapters IX to XI on the Gingival Sulcus and Epithelial Attachment, Eruption of the Tooth and Shedding of the Deciduous Teeth. A closing Chapter XVI on Histologic Technic is appended. The marginal indices are helpful in reviewing the contents of the chapters. A concise review of the newer concept of amelogenesis is clearly expounded. The photomicrography is excellent and the publishers must be complimented for the general appearance of the book, as well as the accurate reproduction of the photomicrographs. We wonder if a discussion of the lymphatic system draining the oral tissues would not have been an appropriate addition to the book.

We heartily recommend this Oral Histology and Embryology to the student and practitioner alike. H. C.

HISTORY OF MINERS' DISEASES. By GEORGE ROSEN, M.D. Introduction by HENRY E. SIGERIST, M.D. Pp. 490; many figures and tables. New York: Schuman's, 1943. Price, $8.50.

THE seven years spent by the author in the preparation of this monograph have been well rewarded. His purpose of presenting "a comprehensive historical study of miners' diseases from prehistoric times to the end of the 19th century" has been well fulfilled, so that the student of the subject will find much solid information—both historical, sociologic and economic—while the more casual reader will find considerable entertainment. The latter will find more of interest in the first third of the book—Part 1, From Neolithic Times to the End of the 18th Century, and may be pardoned for skipping long stretches of Part 2, especially the often dreary analyses of relatively unimportant reports included in the 170 pages of Pathology and Nosography. Dr. Rosen has rightly decided that (in Sigerist's introductory words) "The history of occupational diseases is infinitely more than medical history," and that, here especially, "whether any use was made of medical knowledge did not depend so much on the physicians, as on the social organization under which the laborer performed his work." There are important chapters, therefore, on Mining and Miners, Morbidity and Mortality Statistics, The Beginnings of Social and Protective Legislation, as well as on the more strictly medical aspects.

One's regret that the study stops with the end of the 19th century, and

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thus incidentally includes nothing about American mining, is tempered by the author's expressed hope that, under more propitious circumstances, he will present a similar study of the first four decades of the 20th century. At that time, also, he can cover asbestosis, silicosis, miner's nystagmus, miner's anemia and cancer of the lung, as adequately as he has presented anthracosis in this volume.

One wishes, too, that such a well-prepared book could have been more lavishly illustrated. The 8 illustrations from Agricola's *De Re Metallica* might have set a standard that would have at least tripled the number of the fascinating 3 pre-Agricola pictures, and quadrupled those of the later period. Certainly the 2 pictures taken from Snell and from the Report of the Royal Commision of 1842 tell more vividly and emphatically than pages of text, the need at that time for drastic change. They should make us, too, more understanding and therefore more tolerant of organized labor's present abuse of its opportunities, now that it is having its innings.

As a final recommendation of this and similar efforts, when well done, we may quote Sigerist's final paragraph: "The historical presentation of a problem that has been solved is interesting enough because it illustrates the long way that had to be gone before the goal was reached. But when a job is not finished then the historical analysis becomes the more significant. By revealing the factors involved, those that retard and those that accelerate developments, it helps us to act more intelligently and thus paves the way into the future." E. K.

TEXTBOOK OF ANATOMY AND PHYSIOLOGY. By CATHERINE PARKER ANTHONY, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital, Cleveland, Ohio; Formerly Instructor of Anatomy and Physiology, Frances Payne Bolton School of Nursing, Western Reserve Univ. Pp. 400; 35 tables; 153 illus. (8 color plates). St. Louis: C. V. Mosby, 1944. Price, $3.50.

THIS textbook in Anatomy and Physiology intended for preclinical nursing students is planned for a course of 90 to 100 hours. The text presents the essentials of anatomy and physiology, using a plan which conserves the instructor's time in preparation and facilitates the student's learning. The topical outlines preceding each chapter develop the subject matter in a logical way by the use of clear tables, diagrams and pictures. A compact outline summarizes each chapter. Stimulating review questions follow. Prepared examinations for each chapter and an answer key are also provided.

This text is a valuable contribution to nursing education, being especially adaptable to the school of nursing with a limited teaching personnel. While not planned for a reference or research book, it contains all the essential concepts of anatomy and physiology necessary for preclinical students.

H. F.

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By GEORGE R. HERRMANN, M.S., M.D., PH.D., F.A.C.P., Professor of Medicine, Univ. of Texas; Director of the Cardiovascular Service, John Sealy Hospital Consultant in Vascular Diseases, U. S. Marine Hospital. Third ed. Pp. 516; 103 figs.; numerous tables; 103 illus. (4 color plates). St. Louis: C. V. Mosby, 1944. Price, $5.00.

THIS handbook of cardiovascular diseases has been useful and popular. It demonstrates well how a large body of information can be presented in a concise and easily understandable manner. These characteristics have been retained in the 3rd edition. There have been some rearrangements made and new sections added which are pertinent to this field in relation to the war. Such are a description of the immersion foot syndrome, and a chapter on Military Cardiovascular Examinations and Interpretations. Of considerable interest, also, is an Appendix which describes new electrocardiographic data obtained with the use of unipolar central terminal precardial leads. The illustrations throughout the book are excellent. The pressure of accelerated

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teaching programs will undoubtedly enhance the value of this book to teachers and students. The busy practitioner will find it helpful in clarifying some of the problems with which he is faced. L. A.

PHYSICAL BIOCHEMISTRY. By HENRY B. BULL, PH.D., Associate Professor of Physiological Chemistry, Medical School of Northwestern Univ. Pp. 347; 93 figs.; 44 tables. London: Chapman & Hall; New York: John Wiley & Sons, 1943. Price, $3.75.

IT is sometimes the pleasure of a Reviewer to be, in essence, an advertiser, albeit one whose sincerity may by the very nature of things be taken for granted. So it is that in this case the Reviewer, having found himself a whit less ignorant for the study of his subject, would urge his fellows to do the same.

Dr. Bull has here presented the working methods of thought of one of the most basic sciences, without whose language at the very least the modern investigator is increasingly helpless and limited. The derivations are presented rather in outline than in full, but ample references are supplied. This has the virtue of allowing a book of moderate length to survey a vast field. Some may find grounds for criticism when highly complex mathematical equations are introduced "out of the blue," or adjacent to simpler ones. Since such equations are uniformly pertinent and necessary to the subsequent discussion, the reader has the choice of accepting what is given or following it out in the literature. In the chapter on electrostatics, Poisson's equation for the relation between potential and charge is an example. It is the Reviewer's feeling that this limitation is inherent in the outline, or survey method of discussion, and needs no defense. It may further be held that many surveys, by their brevity, leave nothing applicable in their wakes; Dr. Bull steers skilfully between the Scylla of sketchiness and the Charybdis of unwieldly length, leaving the reader with an extremely useful system of thought, some knowledge of experimental method, and one of the best bibliographies in the field.

It lends concreteness to the discussion and orients the prospective reader to glance briefly at some of the material covered. A preliminary discussion of atomic structure leads to a consideration of isotopes, molecular structure and the nature of chemical bonds. The section on thermodynamics wisely emphasizes the practice of dimensional analysis of equations, and then leads off with a simple and useful presentation of entropy, an understanding of which is so often difficult for the student. The subsequent development of the expressions for energy change and activities is easily followed and of immediate applicability to biologic problems. The chapter on reaction kinetics leads into the heart of quantitative biologic measurements with a thorough discussion of reactions catalyzed by enzymes. The section on dialectrics reviews a field complex in nature, and difficult of discussion, which is vital to structural organic chemistry. In this case, the reader must be tolerant enough, if critical of the brevity, to remember the purpose of the book; sufficient material is presented for the understanding of subsequent sections. The highlight of the chapter on ions in solution is an able development of the Debys-Huckel theory of interionic attraction, called by the author one of the most important contributions to chemistry in this century.

It must suffice merely to mention some of the remainder of the 18 chapters. These include discussions of acids and bases, oxidation-reduction, electrokinetics (with a clear explanation of electrophoretic techniques), interfacial problems, colloidal solutions, membranes, and other related subjects.

There is throughout the book a sense of well-disciplined thought and exacting analysis which leaves the reader well grounded for further and more detailed study, and well fitted for the critical improvement of his own experimental approach. As a scientist of extensive training and experience, Dr. Bull gives here the tools with which the exact investigator may vastly improve himself. If he be already conversant with physical chemistry, he will find new order and clarity for his mental workshop—if not, he will search long and far for a better introductory course. B. R.

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MOTIVATION AND VISUAL FACTORS. By IRVING E. BENDER, HENRY A. IMUS, JOHN W. M. ROTHNEY, CAMILLA KEMPLE, and MARY R. ENGLAND. Pp. 369. Dartmouth Coll. Pubs., 1942. Price, $4.00.

COMPLETE visual examinations were made during the 4 years of the college course on students entering Dartmouth University beginning with the fall of 1936. Data of psychologic factors and motivation were obtained during the students' senior year by interviews, autobiographies, projective techniques and so forth. On the basis of these varied data, a detailed presentation is made of the motivational pattern of 20 representative students under various visual classifications in order to show the relevance of the visual factor in the light of the total personality. For each case there is given a summary of the general data, a visual summary, a psycho-portrait of the student, and finally a brief description of the rôle of the visual factors, in view of the motivational structure of the individual. The authors point out that their results must be interpreted as being restricted to the special population studied, for among Dartmouth students visual handicaps are rare, and none of those who were examined were functionally handicapped to any considerable degree. Further, all those who needed glasses were provided with adequate correction. It is further pointed out that the results obtained are only a contemporary study of motivation, since no attempt was made to study the influence of the visual defects upon motivation in the early life of the individual.

The authors conclude that it is not possible to draw any conclusion regarding the influence of visual defects on the motivational pattern of the individual. However, the evidence does indicate that the motivational pattern of the individual influences his adjustment to his visual condition. The findings indicate that it is important to correct visual defects which interfere with visual comfort and with the visual efficiency of the subject. This book is of far more interest and importance to those who are concerned with the psychologic background of the students than with the visual defect. F. A.

THE GENEALOGY OF GYNÆCOLOGY. History of the Development of Gynæcology Throughout the Ages, 2000 B.C.–1800 A.D., with excerpts from the many authors who have contributed to the various phases of the subject. By JAMES V. RICCI, A.B., M.D., Associate Clinical Professor of Gynecology and Obstetrics, New York Medical Coll.; Director of Gynecology of the City Hospital, New York; Associate Attending Gynecologist and Obstetrician, Flower and Fifth Avenue Hospitals, New York; Consultant in Gynecology and Obstetrics, Broad St. Hospital; Fellow of the New York Academy of Medicine. Pp. 578; 54 figs. Philadelphia: Blakiston, 1943. Price, $8.50.

A COLLEAGUE who knows medical history, having been asked recently where he would place the chronologic mid-point of medical history, *i. e.*, the data which would divide medical progress into two equal halves, answered, "Oh, about 50 years ago." We both were sure that such a date would fall on this side of the year 1800. If either of these is correct, a survey, such as Ricci's Genealogy, misses half or more of the story. In fact, it would be hard to accept, if one did not see the Footnote on p. xviii of Dr. Schumann's Introduction, telling us that a second volume on modern gynecology was to follow.

This said, one can be free with praise of this full, well-documented narrative, modestly told, but clearly representing years of patient labor that doubtless would have been laborious if it were not, as is obvious, a labor of love. The author, a teacher and practitioner of gynecology and obstetrics, more than an historian, makes no pretense at original research, and "as a child in scholarship" has "leaned heavily on the monumental compilations of the master, medical historians," as may be verified in the character of the references. In fact, one might add that volumes such as this, directed at the reader who is not a professional historian himself, possesses certain advantages when not composed by the professional historian; and there are practically no medical histories in English, general or special, by professional medical histor-

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ians, anyhow; on gynecology and obstetrics, Jameson's small volume in the Clio-Medica Series is the only one I know of in English.

The author follows the conventional chronologic approach: The Prehistoric Period; The Ancient Epoch (Egyptian, Babylonian, Assyrian, Hindu, Hebrew); The Classic Age; The Byzantine Period; The Arabic Era; The Mediaeval Epoch; The Transitional Period (Renaissance, 17th and 18th centuries)—a part about as long as all the preceding parts together. An Index of 64 double columns in small print shows the detailed and conscientious way in which this book had been prepared; and yet the Subject Index (of 12 columns) could well be much larger still. The Index of Personal Names shows how many past writers can be found here, and only here among medical histories.

The references are conveniently placed for the reader at the bottom of each page, in addition to a Bibliography at the end of each chapter. They not infrequently, however, refer to a translator or commentator rather than to the original source, or may not be sufficiently "complete" to lead to the source, without further search; the names of authors of Latin works may be misspelled or appear in the genitive case, errors of typography are more than average. These are but minor criticisms, however, and we know of no other history of this subject in English that compares with this work in its fulness, yet readability, its richness of illustrations, its documentation, and its guides to further reading. For the clinician and layman aware of medico-historical values, this narrative is highly recommended; for all, it is a valuable reference work that leads to a rich list of sources. E. K.

THE COMPLETE PEDIATRICIAN. By W. C. DAVISON, Professor of Pediatrics, Duke Univ. School of Medicine; Formerly Acting Pediatrician in Charge, The Johns Hopkins Hospital. Fourth ed. Durham, N. C.: Printed by Seeman Printery for Duke Univ. Press, 1943. Price, $3.75 by check; $4.00 on credit.

"THIS 4th edition, in which 7000 lines were changed, was written because of the accumulation of additional pediatric information during the past 3 years, particularly in chemotherapy, infectious and tropical diseases . . . ." This well-known handbook now contains 13 chapters divided into a total of 250 sections, and a score of orderly, helpful tables. The first 7 chapters are composed of organized lists of the symptoms and signs produced by diseases of the major organ systems, with notes on the diseases and on treatment. The remaining chapters discuss laboratory and other procedures frequently used in pediatrics; nutritional requirements; feeding and diets; therapy and pediatric nursing; growth, development and child care; history taking and physical examination; and drugs and prescriptions. There are innumerable cross-references.

The author deems lactic acid milk the optimal base for artificial infant feeding. Planned for "medical students, internes, general practitioners and pediatricians," the book is a comprehensive summary of facts pediatric, judiciously compiled and easy to use. I. W.

NEW BOOKS

Tuberculosis of the Ear, Nose, and Throat: Including the Larynx, the Trachea, and the Bronchi. By MERVIN C. MYERSON, M.D. Dedication to DR. HUBERT ARROWSMITH, Pioneer in Bronchoscopy and Laryngology. An outstanding worker in the field of tuberculosis. Pp. 291; 89 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $5.50.

THIS should be in the hands of all who work with institutional tuberculous patients and is of value to all who practice otolaryngology. The Author has presented the subject in a clear, concise, yet adequately comprehensive manner. Diagnostic and therapeutic procedures are discussed in detail. The book is well illustrated and contains an excellent bibliography. K. H.

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Psychiatry and the War. A Survey of the Significance of Psychiatry and Its Relation to Disturbances in Human Behavior to Help Provide for the Present War Effort and for Post War Needs. Edited by FRANK J. SLADEN, M.D., Physician-in-Chief, Henry Ford Hospital, Detroit Trustee, McGregor Fund. Contributions of the Conference on Psychiatry of the University of Michigan and McGregor Fund. Pp. 505. Springfield, Ill.: Charles C Thomas, 1943. Price, $5.00.

Experimental Spectroscopy. By RALPH A. SAWYER, PH.D., Professor of Physics, University of Michigan. Now Lt. Comdr., U.S.N.R. and on leave from the Univ. of Michigan. Pp. 323; 107 figs. New York: Prentice-Hall, 1944. Price, $6.00.

Infections of the Peritoneum. By BERNARD STEINBERG, M.D., Director of Toledo Hospital Institute of Medical Research; Past Fellow of the National Research Council; Former Crile Research Fellow, Western Reserve Univ. Foreword by FREDERICK A. COLLER, M.S., M.D., Professor of Surgery, Univ. of Michigan Medical School; Director, Dept. of Surgery, University Hospital, Ann Arbor, Mich. Pp. 455; 45 figs.; 21 tables. New York and London: Paul B. Hoeber, 1944. Price, $8.00.

Caesarean Section. The History and Development of the Operation From Earliest Times. By J. H. YOUNG, M.B., CH.B., D.T.M. and H. (EDIN.). Foreword by MILES H. PHILLIPS, M.D. (HON.), B.S., F.R.C.S., F.K.C.O.G. Pp. 254; 22 tables. London: H. K. Lewis, 1944. Price, 16 Shillings.

Principles and Practices of Inhalational Therapy. By ALVAN L. BARACH, M.D., Associate Professor of Clinical Medicine, Columbia Coll. of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital. Pp. 315; 59 figs. Philadelphia: J. B. Lippincott, 1944. Price, $4.00.

Physical Medicine in General Practice. By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mount Sinai Hospital; Assistant Clinical Professor of Therapeutics, New York Univ. Medical Coll., New York. Pp. 643; 310 figs. New York and London: Paul B. Hoeber, 1944. Price, $7.50.

Hydronephrosis and Pyelitis (Pyelonephritis) *of Pregnancy.* Etiology and Pathogenesis. An Historical Review. By H. E. ROBERTSON, M.D. Philadelphia: W. B. Saunders, 1944. Price, $4.50.

The Neurosurgical Patient. His Problems of Diagnosis and Care. By CARL W. RAND, Clinical Professor of Neurological Surgery, Univ. of Southern California, School of Medicine, Los Angeles, Calif. Pp. 576; 121 figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $4.00.

Secretory Mechanism of the Digestive Glands. By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C., Research Professor of Physiology, McGill Univ., Montreal, Canada; Formerly Professor of Physiology in the Univ. of Odessa, Russia, and in Dalhousie Univ., Halifax, Nova Scotia, Canada. Dedication to DR. CHARLES F. MARTIN, Emeritus Dean of Medical Faculty of McGill Univ. Pp. 900; 220 illus. New York and London: Paul B. Hoeber, 1944. Price, $12.75.

The Electrocardiogram. Its Interpretation and Clinical Application. By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island and Harbor Hospitals; formerly Instructor in Medicine, New York Post-Graduate Medical School, Columbia Univ. Pp. 403; 203 illus. and plates. New York: Grune & Stratton, 1944. Price, $7.50.

Artificial Pneumothorax in Pulmonary Tuberculosis. Including Its Relationship to the Broader Aspects of Collapse Therapy. By T. N. RAFFERTY, M.D., Phoenix, Ariz. Formerly Resident Physician, William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Mich. Introduction by HENRY STUART WILLIS, M.A., M.D., Supt. and Medical Director, William H. Maybury Sanatorium, Northville, Mich. Pp. 192; 26 illus. New York: Grune & Stratton, 1944. Price, $4.00.

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The Pathogenesis of Tuberculosis. By ARNOLD R. RICH, M.D., Associate Professor of Pathology, The Johns Hopkins Univ. School of Medicine, Baltimore, Md. Pp. 1008; 89 figs.; 4 charts; 20 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, $10.50.

The Analysis and Interpretation of Symptoms. Edited by CYRIL M. MACBRYDE, M.D., and 10 contributors. Reprinted from *Clinics*, April, 1944, vol. II, No. 6. Pp. 1343 to 1644; numerous figs., tables and plates. Philadelphia: J. B. Lippincott, 1944. Price, $4.00.

The Medical Clinics of North America. New York Number. Symposium on Psychosomatic Medicine. By 18 contributors. Pp. 787; 62 figs. Philadelphia and London: W. B. Saunders, 1944.

NEW EDITIONS

American Men of Science. A Biographical Directory. Edited by JACQUES CATTELL. Seventh Ed. Pp. 2003. Lancaster, Pa.: The Science Press, 1944. Price, $14.00.

Colorimetric Determination of Traces of Metals. By E. B. SANDELL, PH.D., Assistant Professor of Analytical Chemistry, Univ. of Minnesota, Minneapolis, Minn. Vol. 3. Pp. 487; 73 figs.; 66 tables. New York: Interscience Publishers, 1944. Price, $7.00.

The Diabetic Life. Its Control by Diet and Insulin. A Concise Practical Manual for Practitioners and Patients. By R. D. LAWRENCE, M.A., M.D., F.R.C.P. (LOND.), Physician-in-charge of Diabetic Department, King's College Hospital; late Chemical Pathologist and Lecturer in Chemical Pathology, King's College Hospital. Thirteenth ed. Pp. 228; 18 figs. Philadelphia: Blakiston Company, 1944. Price, $4.00.

Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the Univ. of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital; Consultant in Ophthalmology, Philadelphia Hospital for Insane (Byberry); Assistant Ophthalmologist in the Rush Hospital, Philadelphia. Third ed. Pp. 934; 798 figs.; 6 color plates. Philadelphia: Lea & Febiger, 1944. Price, $11.00.

THE fact that a new edition was necessary just 3 years after the publication of the 2nd edition, is added testimony to the popularity and value of this work. The new additions include a discussion on the physiology of squint and a clarification of the section on ptosis. The illustrations, print and binding are excellent. F. A.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author is the manuscript is accepted.

For the balance of the war, 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

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